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I. ON RENAL RETINITIS IN YOUNG SUBJECTS AND ON THE RELATIVE FREQUENCY OF JUVENILE INTERSTITIAL NEPHRITIS IN THE TWO SEXES.

By E. NETTLESHIP.

IN a paper upon the ocular changes that occur in renal disease in vol. xv, Part IV of these Reports, a short statement was made as to albuminuric retinitis in children and young subjects. The scanty data I had then had the opportunity of collecting suggested that the subject, if followed up, might reveal points that would be of interest to physicians in their researches upon chronic nephritis in children, and especially the interstitial forms of that disease.

Owing to the kindness of the staff of the Hospital for Sick Children, Great Ormond Street, I have been able to search the in-patient and *post-mortem* books of that Institution from 1864 to 1903, and have obtained much valuable material. My best thanks are also due to Dr. H. P. Hawkins, Dr. Leonard Guthrie, Dr. George A. Sutherland, Dr. J. E. H. Sawyer, Dr. George Carpenter, Dr. Miles Miley, and others, for information, and for leave to make use of cases. I am especially indebted to Dr. J. E. H. Sawyer's elaborate paper on "Chronic Interstitial Nephritis in Children,"* published

* J. E. H. Sawyer, The Birmingham Medical Review, August and September, 1903.

almost at the same time as my paper on renal retinitis above mentioned, for references to additional cases. I have also found some published cases not referred to by any of the above writers. Some of Dr. Sawyer's cases were obtained, like some of mine, from the Hospital for Sick Children, but I have taken care not to count any of these twice.

From the above-mentioned, and various other, sources, just 80 cases of interstitial nephritis* in patients not more than 21 years of age have been collected, including 9 cases of my own given in greater or less detail in the paper already referred to. In addition, I have found 3 cases in which the chronic nephritis was associated with calculus in kidney or bladder; if we counted these the total would be 83.

Of the total number the date of death is known in 62, and in 60 a *post-mortem* examination was made. In the remainder the issue was not fatal, or the date of death could not be ascertained, and in reckoning these as examples of granular or interstitial nephritis I have been guided by the recorded diagnosis, or, when the written heading to an unpublished case was inconclusive, I have taken the evidence afforded by the notes.

This collection of cases of granular or interstitial nephritis is obviously by no means uniform. The want of homogeneity is owing, no doubt, in a few instances to mistakes in my choice of cases, but much more to the fact that death does not always occur at the same stage of the kidney disease, and possibly to the inclusion, unavoidable at present, of more than one pathological species. Upon such pathological points I am not competent to speak; but it is clear from published cases that, *e.g.*, the natural history of the acute interstitial nephritis of infants has not yet been fully worked out, and that its relation to the extreme forms of granular contracted kidney from which elder children

* I have made no attempt to separate the "true granular contracted" from the "small white" kidney; and I have included cases of early interstitial nephritis.

occasionally suffer is at the present time more a matter of inference than proof.

But whatever subdivisions it might be possible to make in the 80 cases that I have classed as interstitial nephritis, that group can certainly, as a whole, be separated clearly from the parenchymatous series. Keeping the two classes distinct, I have tried in what follows to ascertain, without going beyond what may be included within the ophthalmologist's purview, whether anything can be made out by a comparison between them that may throw light upon the etiology of interstitial nephritis in children.

For purposes of comparison I have, therefore, examined the notes of all the cases diagnosed as parenchymatous nephritis, or inferred from the notes to be of that nature, at the Hospital for Sick Children,* omitting all very recent cases of scarlatinal nephritis, and also the cases (7 in number) of well-marked amyloid disease. In this way a series of 149 cases has been obtained. Fifty-six of these were fatal, and in 50 a *post-mortem* examination was made.

Retinitis, or multiple retinal hæmorrhage, was observed in 31 of the 80 cases of interstitial nephritis, and in 2 out of the 3 examples of granular or contracted kidney associated with calculus. The eyes were examined, and found normal in about 10 others. In the remainder (about 37) no ophthalmoscopic examination seems to have been made.

Amongst the 149 parenchymatous cases definite retinitis was found in 7, and doubtful appearances—such as slight haziness of the discs—of uncertain significance, in several more. In about 43 the eyes were examined and found normal, and in the remaining 90 there was apparently no ophthalmoscopic examination.

In the 7 cases of amyloid disease the ophthalmoscope seems to have been used to only 1, and in that 1 the fundi were normal.

* Increased by some 20 to 30 cases published or communicated by Dr. Miles Miley and others.

Amongst the total number of 40 cases of retinitis in both groups, the number in which the eye changes were very severe was larger than in any similar consecutive number of cases in older subjects. Both retinae were detached in 3 patients, very abundant hæmorrhage formed a marked feature in 2 or 3 others, whilst the exudation and swelling were excessive in 3 or 4 more. But we must not hastily conclude from this result that the ocular changes are especially liable to reach an unusually high degree in the young; for it is likely enough that milder degrees of retinitis causing little interference with sight would have been discovered in a good many more of the children had the ophthalmoscope been used by routine.

A similar remark applies to the apparent scarcity of retinal changes in parenchymatous as compared with interstitial nephritis in the young—the ophthalmoscope was used much less frequently in the parenchymatous cases than in the others.

The earliest age at which renal retinitis has been recorded seems to be 5 years (Bull's case, a girl).* Amongst 40 cases (interstitial and parenchymatous) I find 2 cases æt. 7 years, 3 of 8 years, 2 of about 9, 3 of 10, 2 of 11, 5 of 12, or in all about 18 below the age of 13 years. Rather more than half of the series (23 cases) were æt. from 14 to 21 years. Twenty-six of the whole number were females, 14 males.

Of these 40 young patients with retinitis, 24 died at a known interval after the eye condition was first discovered. This interval was $3\frac{1}{2}$ years in 1 case,† between 12 and 15 months in 4 cases, between 4 and 7 months in 3 cases, and less than 4 months in 16 cases.

From the data at present available it appears, therefore, that the prognostic importance of the retinal changes in chronic renal disease is certainly not less grave, perhaps

*. Two cases at the Great Ormond Street Hospital, æt. 4 and 5 years respectively, showed slight questionable appearances of neuro-retinitis.

Case of Theresa R. in my previous paper, p. 330.—E. N.

more so, in children and young subjects than it has long been known to be in adults.*

In my previous paper I found that chronic renal disease occurring below the age of 21 was commoner in females than males, exactly the reverse of the rule obtaining for older subjects; but the number of cases then counted was too small to allow of any but a provisional conclusion on such a point. The same fact, an excess of females over males, was also observed by Sawyer and was remarked upon by Handford as long ago as 1890. On examining the entire series of 80 cases this conclusion is strongly confirmed, the females being to the males as 51 to 28,† (64 and 36 per cent.) or nearly twice as many females as males.

In order to ascertain whether the relative frequency of the sexes is the same in the parenchymatous as in the interstitial disease we must compare cases of the same age in each series. This I can do by taking only those of both kinds, interstitial and parenchymatous, below, say, 13 years of age, that being about the maximum age allowed at the children's hospitals. My parenchymatous series below the age of 13, consists of 130 cases; of this number 70 are males (54 per cent.), and 60 females (46 per cent.), a slight but decided excess of males. Dickinson using partly the same material, found nearly the same proportions. Of the entire interstitial nephritis series, 51 patients were less than 13 years old, and of these 16 (about 30 per cent.) were males and 35 (nearly 70 per cent.) females, an even larger excess of females than is found when the cases aged from 13 to 21 years are included. Though these numbers are comparatively small they confirm the earlier provisional conclusion arrived at by Sawyer and myself, *viz.*, that interstitial nephritis in the young is much more frequent in females than males. They show further that the same does

* See Marcus Gunn, Trans. of Ophth. Soc.; Miles Miley, *ibid.*; Bull and others.

† In the remaining case the sex is not mentioned.

not hold good in parenchymatous nephritis at the corresponding ages, where the males are slightly in excess.

It would be easy for anyone, who could give the necessary time, to examine a much larger number of cases of parenchymatous nephritis in young persons, and confirm or refute my finding as regards the sex liability in this class, for parenchymatous nephritis is sufficiently common in children. In the meantime we may note that, whilst the figures given above show that there is some excess of males over females in children suffering from this form of chronic nephritis, the inequality is much less than in adults.*

This marked excess of females over males in the interstitial cases in young subjects, contrasting as it does so strongly with the excess of males in adults suffering from the same form of disease, and the greater or less excess of males in both adults and children in the parenchymatous forms, is certainly very striking. The explanation of such an unexpected fact must be left for future research. The reason certainly cannot be found in the greater exposure to weather, lead poisoning and alcohol of the more affected (*i.e.*, female) sex; and apparently not in any special influence of puberty in the female, since the preponderance of females over males seems, as already stated, to be less between the ages of 13 and 21 than it is below the age of 13 years.†

Can a partial explanation be found in a corresponding excess of girls over boys born syphilitic and surviving early infancy?‡, or in differences of frequency or character in scarlet fever as it affects the two sexes?§

* In adults, according to Dickinson, tubal and diffuse nephritis is more than twice as frequent in males than in females.

† I have 27 cases of interstitial nephritis in patients æt. from 13 to 21, and of these 15 were females, 12 males.

‡ In respect to sex in the subjects of inherited syphilis, Hutchinson states, in his classical monograph (1863), that of 102 patients with interstitial keratitis, 64 were females and 38 males, or about 63 and 37 per cent. respectively.

In 564 consecutive cases of the same eye malady, I find 339 females and 225 males, or 60 and 40 per cent. respectively.

§ In regard to scarlet fever, Dickinson, in discussing the reasons for the

The view that congenital syphilis is often the cause of acute infantile nephritis, usually interstitial, appears to be gaining ground. Future observations may be expected to decide the question whether, when such infants survive, they sometimes die in their teens from advanced granular kidney disease, and also, if this be so, whether they generally show the common dental and facial sign of hereditary syphilis? Very little is to be found in the notes of cases of juvenile granular kidney as to the condition of the permanent teeth or the physiognomy, a piece of negative evidence that I think cannot be entirely accounted for by defective note-taking.

It may save trouble to future workers if I take out the facts as to scarlet fever and some other reputed causes of granular kidney in children now that the records of a number of cases are before me. In upwards of 30 of the 80 cases the notes of previous history at my disposal were incomplete, leaving about 45 for use in this connection.

Scarlet fever is stated to have occurred before renal symptoms began, in 16 of these 45 cases from the granular kidney series (13 girls, 3 boys) the interval between the fever and the recognised renal symptoms being never less than about 2 years, and often much more. In at least 6 cases scarlet fever was definitely denied.

Measles alone, or with the added effect of chicken-pox, was assigned as, or seemed to be, the most probable cause in about 8 cases.

In 1 case there was a history of an unnamed fever; in 2, severe prolonged infantile eczema;* in 2, severe infantile diarrhoea; in 1 or 2 rickets, arrest of growth and subsequent failure of intelligence. In 3 cases there was a clear history

excess of males over females in chronic nephritis as a whole, and also in fatal scarlatinal dropsy, adds "it is to be observed at the same time that the deaths from scarlatina are nearly the same for both sexes." "Diseases of the Kidney and Urinary Derangements," Part II, pp. 267 and 321 (1877).

* Eczema also appeared to be the cause in 2 of the parenchymatous cases.

of stone in the kidney and bladder. In 3 cases alcohol was presumably the cause, 2 being lads who drank heavily, 1 a young barmaid who owned to taking neat brandy before breakfast and was a large meat eater.

Hereditary syphilis was proved in only 6 cases of interstitial nephritis, 3 of these being infants; but it was highly probable in several others. It was certainly the cause in 4 of the parenchymatous cases. This rather meagre record of facts, in contradistinction to opinion as regards congenital syphilis, points to the need for much more careful inquiries in future.

In several of the 45 granular cases all history of previous illnesses was denied, but a history was given of polyuria and thirst dating from early infancy.

From the above it seems that one or another of the specific fevers, including syphilis amongst them, might be assigned as the cause of interstitial nephritis of children in at least 31 out of 45 cases, whilst some other profound disturbance of infantile health had preceded the appearance of renal symptoms in several others.

It appears that the same specific fevers may be claimed with something like the same frequency as the cause of parenchymatous nephritis in young subjects, *e.g.*, in at least 45 of 150 cases, a proportion representing, however, much less than the whole truth, since the clinical history at my disposal was even more frequently incomplete in the parenchymatous than the interstitial cases.

REFERENCES TO THE CASES OF CHRONIC NEPHRITIS IN YOUNG SUBJECTS.

1. 1864. HULKE. Roy. Lond. Ophth. Hosp. Reports, 1 case.
vol. v, p. 20.
2. 1871. HUTCHINSON. The Lancet, vol. i, p. 479 .. 1 „
3. 1873. JABEZ HOGG. The Lancet, vol. ii, p. 701 .. 1 „
4. 1873. MAGNUS. Albuminurie in Ihre Ophthalmoscopischer Erscheinungen. 2 cases.
5. 1874. W. H. BARLOW. The Lancet, vol. ii, pp. 151, 192 1 case.

6. 1877. DICKINSON. "Diseases of the Kidney and Urinary Derangements," Part II, Albuminuria, pp. 376 and 427; 4 cases, 1 of which (A. R., æt. 10) is republished by Sawyer as his Case 3 (see below). 4 cases.
7. 1872. GULL and SUTTON. *Medico-Chirurg. Trans.*, vol. lv, p. 301. 1 case.
8. 1879. GOWERS. *Medical Ophthalmoscopy*, p. 302 .. 1 "
9. 1883. ARTHUR H. BENSON. *Trans. of the Academy of Medicine, Ireland*. 1 "
10. 1886. C. STEDMAN BULL. *Trans. of American Ophthalmological Society*, vol. iv, p. 184. 1 "
11. 1888. JAMES ANDERSON. *Trans. Ophthalmological Society of United Kingdom*, vol. viii, p. 141. 1 "
12. 1888. MILES MILEY. *Ibid.*, p. 135 2 cases.
13. 1889. GEORGE CARPENTER. "Syphilis of Children in Everyday Practice." Repeated in *Reps. Soc. Study of Disease in Children*, vol. iii, p. 287 (1903). 1 case.
14. 1889. HENOCB. *Lectures on Diseases of Children*, vol. ii. (New Sydenham Society). 1 "
15. 1890. H. HANDFORD. *Trans. Pathological Soc. of London*, vol. xli, p. 165. 1 "
16. 1890. HALE WHITE. *Ibid* 1 "
17. 1890. W. J. COLLINS. *Trans. Ophthalmological Soc., United Kingdom*, vol. x, p. 148. 1 "
18. 1890. GOODHART. *Keating's Cyclop.*, "Diseases of Children," vol. iii. 5 cases.
- 18a. 1894. MASSALANGO. *Medical Record*, p. 534.. .. 1 case.
19. 1895. BEAUMONT. *British Med. Jour.*, vol. i, (April 20) 1 "
20. 1897. EMMETT HOLT. *Archives of Pediatrics*, vol. iv, p. 1 (23 cases of primary nephritis in infants). Of these 23 cases I have only used 6, viz., those in which the sex is given and a *post-mortem* examination was made. Of the 6, 3 were interstitial, 3 parenchymatous.
21. 1897. LEONARD GUTHRIE. *The Lancet*, vol. 1, February 27 and March 13, and *Reports of Society for Study of Disease in Children*, vol. i (January 18, 1901). 1 "
22. 1898. HOLMES SPICER. *Trans. Ophth. Soc., United Kingdom*, vol. xviii, p. 145. 1 "
23. 1899. HOLMES SPICER. *Ibid.*, vol. xix, p. 73.. .. 1 "
24. 1898-99. SUTHERLAND and LAWSON. *Ibid.*, vol. xviii, p. 140, and vol. 19, p. 71. 1 "
25. 1899. A. E. RUSSELL. *St. Thomas's Hospital Reports*, vol. xxviii, p. 63. 2 cases.
26. 1899. GOODHART. *Ashby and Wright's Diseases of Children*, 4th ed.

27. 1900. J. B. LAWFORD. Norris and Oliver's Handbook of Ophthalmology, vol. iv, p. 652. 1 case.
28. 1901. SEQUEIRA. Reps. Soc. Study of Disease in Children, vol. i, p. 17. 1 „
29. 1902. MILLIGAN. *Ibid.*, vol. ii, p. 99 1 „
30. 1902. SYDNEY STEPHENSON. *Ibid.* 1 „
31. 1902. CARPENTER. *Ibid.* 1 „
32. 1901. SCHMIDT-RIMPLER. Graefe-Saemisch Handbuch, Kap. xxii, p. 98. 1 „
33. 1901. GROENOUW. *Ibid.*, p. 99.. .. 1 „
34. 1903. CARPENTER. Reps. Soc. Study of Disease in Children, vol. iii, p. 287 (1 new case, in addition to Reference 13 above). 1 „
35. 1903. JAS. E. H. SAWYER. Birmingham Medical Review, August and September. 5 cases.
36. 1903. NETTLESHIP. Roy. Lond. Ophth. Hosp. Reports, vol. xv. 10 „
(6 given in detail).
37. 1903. SUTHERLAND and WALKER. Reps. Soc. Study of Disease in Children, vol. iii, p. 134. 2 cases.
38. BARTELS. Ziemssen's Cyclop. Practical Medicine, vol. xv, p. 426. 1 case.
39. 1898. FILATOFF. Mal. de L'enfance Trans. by Perier. Male, æt. 12. Typical changes, *post-mortem*. 1 „

Unpublished cases have been kindly communicated by—

- Dr. H. P. HAWKINS 1 new case.
- Dr. G. A. SUTHERLAND 2 new cases.
- Dr. JAS. E. H. SAWYER 4 new cases from Guy's Hospital and the Queen's Hospital, Birmingham.

The staff of the Hospital for Sick Children, Great Ormond Street :—
15 cases of granular disease of the kidney in children. Of these cases 10 are new, and 5 have been already published, viz., 2 by Dr. DICKINSON, 1 by Sir THOMAS BARLOW and Dr. JUDSON BURY, and 2 by Dr. JAS. E. H. SAWYER.

Additional particulars as to certain of the published cases have been added through the kindness of—

- Sir W. J. COLLINS.
- Dr. COLMAN.
- Dr. MILES MILEY.
- Mr. HARTRIDGE.
- Dr. JAS. E. H. SAWYER.
- Dr. C. STEDMAN BULL.

II. OBSERVATIONS ON THE PROGNOSTIC AND DIAGNOSTIC VALUE OF RETINITIS IN DIABETES.

IN a previous paper, already referred to, I mentioned my belief that the presence of retinal changes in a person with diabetes does not point to the probability of early death with the same frequency as does the retinitis of chronic Bright's disease, and I feel sure that others must have had a similar experience.

I am now able, owing chiefly to the courtesy of numerous medical friends, to give some particulars of the duration of life and mode of death in 48 patients with diabetic retinitis, or retinal hæmorrhage, who have been under my care.

The age of these patients ranged from 41 to 79 years. Of the 48 patients, 38 are known to have died. Of this number 9 died within 12 months of the discovery of retinitis or the failure of sight caused by it,* and 11 others during the second year, *i.e.*, 19 died within 2 years of the retinitis being discovered. The remaining 18 died at periods varying between 2 and 8 years, and to this number must be added 10 others, who are known to be, or have been, living at dates varying from 2 to 10 years from the retinitis.†

Thus we find that of the 48 cases no less than 28, or nearly two-thirds, or exactly 60 per cent., lived more than 2 years after the eye disease was found, and only 9, or about one-fifth, died within one year. This is very widely different from the history of ordinary renal retinitis (excluding pregnancy cases), in which I find that in my own cases less than one-third lived 2 years after the retinitis and nearly two-thirds succumbed within 12 months.

* The date of commencement of the fundal changes can seldom be fixed, especially as in these elderly subjects there is often some slowly forming opacity of the lens. But in a few instances the retinitis could be dated with tolerable precision.

† Six of these are now living from 6 to 10 years from my first examination.

The prognosis for life is, therefore, clearly much better in the diabetic cases of all ages than in the renal cases of all ages (excluding those caused by pregnancy).

The great majority of the subjects of diabetic retinal changes are more than 50 when the eye changes occur, and in order to compare the relative significance of the retinitis in this malady and in Bright's disease, cases at the same time of life must be chosen. Such a comparison shows that the relatively more fatal significance of albuminuric retinitis holds as decidedly for the more senile group as for the entire class, and the longer average duration of life in diabetic retinitis must, therefore, be ascribed to the different nature of the two principal maladies rather than, as I tentatively concluded in the earlier communication, to some influence of age as such.* Indeed, the figures indicate that in the diabetic group the prospect of life is certainly not better, but probably rather worse, if the retinitis occurs after 55 than before.

The character of the ocular changes is much less uniform in diabetes than in chronic nephritis, and consequently the diagnosis of diabetes or glycosuria from the presence of retinitis or retinal and vitreous hæmorrhages cannot be made with the same near approach to certainty as it can be from the retinal changes in Bright's disease. In spite of their variability the changes observed in the cases of diabetes are, however, of much assistance in diagnosis, especially in the diabetes of elderly and old persons, in which the general symptoms are often mild, and may easily be overlooked.

The disease of retina, due to diabetes, seems, one may almost say, to be a more local affair than it is in renal disease, for we find that in many of the diabetic cases the retinal degeneration (exudation and hæmorrhage) increases either steadily, or by repeated relapses, even when the general condition of the patient has improved and is

* Of 24 patients, æt. 55 and upwards, with renal retinitis, exactly one-third survived for 2 years. Of 38 with diabetic retinitis, æt. 55 and upwards, rather more than half lived 2 years or more.

continuing to be satisfactory. As regards improvement of vision, therefore, the prognosis in diabetic retinitis should be very guarded.

As examples, the following may be mentioned :—

CASE 14.*—A gentleman, aged 56 when first seen, has now, 10 years later, become nearly blind. He underwent amputation of the leg above the knee for gangrene of the foot with success a year ago, *i.e.*, when he was 65.

CASE 23.—A lady, aged 47, with retinitis and diabetes, lived 8 years afterwards, dying of diabetic coma when 55. Her sight got worse, and she was blind before she died.

CASE 19.—A gentleman, aged 47 when first seen, suffered repeated relapses of large hæmorrhage from retinal vessels, the vitreous finally becoming almost opaque before he died at the age of 50.

CASE 43.—A diabetic lady, whose sight began to fail from retinal, chiefly vascular, changes when she was 45, is now about 52 and in what is called excellent health, but absolutely blind.

Half a dozen other instances could be given in which the vision of patients who lived several years deteriorated more or less before death.

On the other hand, cases can be cited in which vision has kept nearly stationary :—

Case 40 is that of a lady whose retinal mischief occurred when she was about 63 ; she knew that she could control her malady by careful living, but told me she “would rather die of it than give up the things she liked.” She is still living, aged about 67, and her sight, though rather worse, still allows her to read what she wants of the newspaper. She still has glycosuria.

CASE 48.—A gentleman, whose sight failed from diabetic retinitis when he was 67, is now 74 and his vision no worse.

* In my series.

Case 12 is that of a cashier in a bank, whose retinitis occurred when he was 48. He is now 58, in fair health, and his visual condition, though imperfect, has not prevented his promotion to the post of manager.

Case 18.—I extracted a horny yellowish cataract from this lady's left eye when she was 61 years old, having watched it for 4 years before, during all of which time her urine contained sugar, but the lenticular opacity prevented any useful examination of the fundus of either eye. The operation was quite successful, and she retained useful vision till she died 3 or 4 years afterwards; but I found white patches in the retina within a few weeks of the extraction, and felt sure from the appearance that they were not then new.

Case 33.—This gentleman's retina became affected when he was 59; he is now 66, and still passes a certain amount of sugar, but his sight is reported to have deteriorated little, if at all, since I saw him.

Since many of the subjects of diabetes also pass more or less albumin, and doubt has sometimes been expressed as to whether the retinitis of the diabetic was not in reality caused by coincident renal disease, it is worth mentioning that in 24 fatal cases where I have obtained a definite statement of the immediate cause of death, diabetic coma figures in 11, gangrene in 3, sudden heart failure in several, and acute uncontrollable diarrhoea in 1. In 3 others there is some doubt whether the final comatose condition was uræmic or diabetic. Several other cases died from various pulmonary and cardiac complications. Assuming, as we may safely, that a proportion of direct deaths from diabetic coma also occurred amongst the residue of cases whose record is incomplete, there appears to be no ground for doubting that one-half to three-quarters of the subjects of glycosuria, in whom retinal complications occur, die directly from their diabetes and not from any accompanying renal disease, and the presumption in these is that

the ocular mischief is caused by the principal malady. There is also, as has been already stated,* direct evidence that diabetes alone can cause retinitis in cases where the urine is from beginning to end free from albumin.

* Author, *loc. cit.*

PRIMARY CHANCRE OF THE CONJUNCTIVA AND
INTERSTITIAL KERATITIS.

By E. TREACHER COLLINS.

THE following case first came under my care at the Moorfields Hospital on October 27th, 1898.

John Y., æt. 24, complained of a sore on the left lower eyelid, which on examination was found to be indurated, having the characteristic appearance of a hard chancre. It was situated near the inner canthus, at the margin of the lid, more to the inner than the outer surface. The pre-auricular gland on the left side was enlarged.

Iodoform ointment was prescribed for application to the sore, and pills containing 2 grains of hyd. c. cret. and 3 grains of pulv. ipecac. a. to be taken internally three times a day.

On November 12th he was found to have a roseola rash on the skin, which he stated had made its appearance a week previously. He also had an ulcerated sore throat. He was told to take the pills four times a day, and continued with them for 2 months, during which time the rash on the skin disappeared. He then ceased attending.

On June 18th, 1900, he again presented himself, stating that for 2 months his left eye had been inflamed.

There was ciliary injection and an irregular mottled haze of the substance of the cornea, with four areas of vascularity ("salmon-coloured patches") at its margin.

The opacity and vascularity at first extended, but subsequently cleared up.

Primary chancre of the conjunctiva is of rare occurrence. Interstitial keratitis in acquired syphilis is also comparatively rare. I am, however, besides the above case, able to refer to 5 others, all recorded within recent years, in which the two were associated.

In all these cases the keratitis was confined to the eye on the side on which the primary lesion was situated.

Lang recorded in the Trans. Ophth. Soc., vol. xi, 1891, and vol. xii, 1892, the case of a man, æt. 42, who had a chancre of the ocular conjunctiva near the caruncle on the right side.

It was followed by secondary symptoms which disappeared under treatment. A year later the right cornea became affected with interstitial keratitis.

Valude recorded in *Annales d'Oculistique*, January, 1897, the case of a man, æt. 30, who had an indurated chancre at the inner angle of the left eye, followed by roseola and the ordinary train of secondary symptoms. He continued treatment for 2 years; 4 years after the primary lesion interstitial keratitis commenced in the left eye. The affection lasted 1 year, and the right eye did not become involved.

Lawford recorded in the Trans. Ophth. Soc., vol. xx, 1900, the case of a man who had a chancre on the conjunctival surface of the right lower lid. He was treated with mercury.

A sore throat followed, but no rash.

Five months after the first appearance of the primary sore, interstitial keratitis commenced in the right eye. Eight years afterwards, the patient reported his right eye as having got quite well. The left eye had never become affected.

Marlow recorded, in the *Ophthalmic Record*, vol. xiii, No. 3, p. 113, March, 1904, the case of a woman, æt. 54; she had a characteristic chancre in the lower conjunctival retro-tarsal fold of the right eye. The pre-auricular and sub-maxillary glands were enlarged. She was prescribed for in the usual way, but not seen again until 10 years later, then in the right eye there was typical interstitial keratitis. The left eye was unaffected.

The association of these two rare affections in the above group of five cases would seem to imply more than a chance coincidence.

It would suggest that the proximity of the primary lesion in syphilis to the eye pre-disposes it to become subsequently the seat of an interstitial keratitis.

The fact that, in each case, the keratitis occurred in the eye on the side on which the chancre was situated, and, so far as the history of the cases go, on that side only, is further in keeping with this suggestion.

In connection with this subject, I have another case which is worthy of record, but which differs from the others in that the primary lesion was on the lip instead of the lid.

Lizzie T., æt. 25, attended at the Royal London Ophthalmic Hospital on July 2nd, 1900, complaining of inflammation in her left eye, which had commenced a fortnight previously.

On examination of the eye she was found to have well-marked interstitial keratitis, some ciliary injection, and typical greyish, mottled, infiltration of the cornea.

Her right eye was unaffected.

Her teeth were regular and not notched. There was nothing in her physionomy suggestive of inherited syphilis, with the exception of one slight scar at one angle of her mouth.

She was one of a family of seven, all living, and none of whom had suffered from any eye affection.

She stated that 3 years ago she had had a sore on the upper lip, which was a long time in healing. Afterwards she had a bad sore throat, loss of hair, and a few spots on the skin. While her lip was bad, the glands in front of her ears were swollen.

She was treated for the lip at the Richmond Hospital. On inquiry, the house surgeon of that institution informed me that a patient of her name and occupation was entered as having attended in 1897 with a chancre of the lip.

Six months previous to coming to me, she had, she said, a swelling on the front of the skin of her right leg, which got well with treatment.

She only attended at the hospital on the one occasion, and I do not know the subsequent history of her case.

In these six cases of interstitial keratitis, coming on, undoubtedly, in acquired syphilis, it is interesting to note

the remarkable variation in the time which elapsed between the occurrence of the primary lesion and the onset of the ocular trouble. Thus, in one case it was only 5 months, and in another as much as 10 years.

For sake of comparison, the interval in each case may be given as follows:—

Lang's case, interval 1 year.

Valude's case, interval 4 years.

Lawford's case, interval 5 months.

Marlow's case, interval 10 years.

Collins's (1) case, interval $1\frac{7}{12}$ years.

Collins's (11) case, interval 3 years.

THE INNERVATION OF THE PUPIL.

By J. HERBERT PARSONS, Curator.

THE iris consists of a highly vascular membrane, the blood vessels of which are arranged radially. It also contains two muscles, composed of unstriated fibres—the sphincter and the dilatator. Of these, the former is a compact ring of muscle, situated near the pupillary margin; the latter is a thin layer of muscle, situated near the posterior surface, the constituent fibres being arranged radially. Each muscle has a separate and independent motor nerve supply.

The sphincter is innervated by the third cranial nerve, the pupil-constrictor fibres originating in the third nucleus in the floor of the aqueduct of Sylvius, passing out of the mesencephalon in the third nerve, and running in the main trunk of the nerve as far as the orbit. The fibres here pass into the branch which supplies the inferior oblique, leaving it by the short root of the ciliary ganglion. From the ciliary ganglion, they pass by the short ciliary nerves to the eye, piercing the sclerotic around the optic nerve, and forwards in the choroid and ciliary body to the iris.

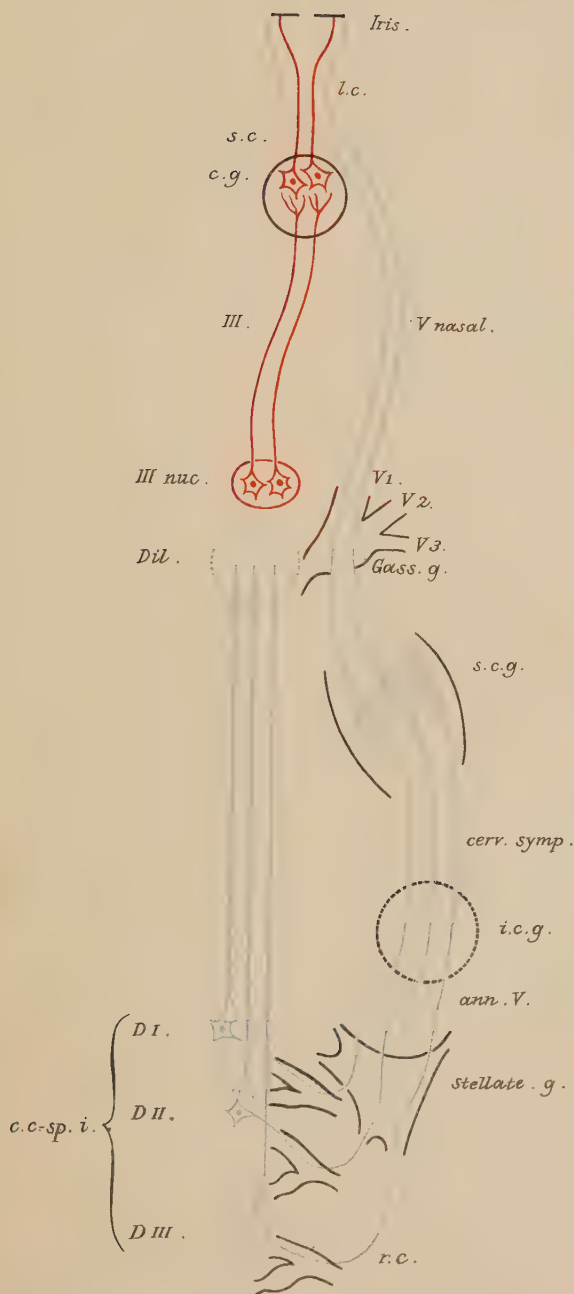
The dilatator pupillæ is supplied by the cervical sympathetic nerve. The dilatator tract probably commences in the neighbourhood of the third nucleus in the mesencephalon, passing through the medulla oblongata, where its exact path is still unknown, into the lateral columns of the cord. The fibres leave the cord by the ventral roots of the first three thoracic nerves (cat, dog, ape), enter the rami communicantes, and run to the first thoracic or stellate ganglion. From here they mostly pass into the anterior limb of the annulus of

PLATE I.

THE EFFERENT PUPILLO-CONSTRUCTOR (RED) AND PUPILLO-DILATOR (BLUE) PATHS.

III. nuc., nucleus of third nerve; *III.* third nerve; *c.g.*, ciliary ganglion
s.c., short ciliary nerves.

Dil., hypothetical dilator centre in medulla; *c.c.sp.i.*, centrum cilio-
spinale inferius; *D I*, *D II*, *D III*, first, second, and third dorsal nerves;
r.c., ramus communicans; *stellate g.*, stellate ganglion; *ann. V.*, annulus of
Vieussens; *i.c.g.*, inferior cervical ganglion; *cerv. symp.*, cervical sympa-
thetic; *s.c.g.* superior cervical ganglion; *Gass. g.*, Gasserian ganglion;
V1, *V2*, *V3*, first second, and third divisions of the fifth nerve; *V nasal*
nasal branch of the ophthalmic (first) division of the fifth nerve; *l.c.*, long
ciliary nerves.



Vieussens, though some run in the posterior limb. They pass up the neck in the cervical sympathetic to the superior cervical ganglion. From here the dilator tract enters the skull by the cervico-Gasserian strand, running independently of the carotid plexus. It joins the Gasserian ganglion, and passes thence into the first or ophthalmic division of the fifth nerve, following the nasal branch, which it leaves finally to enter the long ciliary nerves, thus avoiding the ciliary ganglion. The long ciliary nerves enter the eye on each side of the optic nerve, and running forwards between the choroid and the sclerotic, pass through the ciliary body to be distributed to the iris. (See Plate I.)

These bald statements are the conclusions arrived at as the result of a vast amount of research during the latter part of last century. In many cases the results have been contradictory, or apparently so, but recent work tends to establish the given statements as incontrovertible facts. There are still, however, many unsolved problems, and these are intimately bound up with the apparently contradictory results of the early experiments. No one attacking the subject afresh can afford to ignore these investigations. It will be well, therefore, to give a brief *résumé* of the evidence upon which the principal statements are founded.

THE MECHANISM OF CONSTRICTION AND DILATATION OF THE PUPIL.—Given constrictor and dilator muscles, each with its own independent nerve supply, together with radially disposed blood vessels, it is clear that constriction of the iris may be due to any of three causes:—(1) contraction of the constrictor muscle; (2) relaxation of the dilator muscle; (3) dilatation of the blood vessels. Similarly dilatation may be due to:—(1) contraction of the dilator muscle; (2) relaxation of the constrictor muscle; (3) constriction of the blood vessels. There is ample evidence to support the view that each of these methods is actually brought into use, and that the three causes are effectual in diminishing degree in the order named.

The Dilator Pupillæ.—Histological evidence alone has

not succeeded in demonstrating beyond cavil the existence of a dilator muscle in the iris, but taken in conjunction with the physiological evidence it must now be considered proved. The histological difficulties are to be found in (1) the proof of the presence of radial muscle fibres, other than those in the walls of the vessels; and in (2) the interpretation of the nature of the cells forming the posterior layers of the iris.

Maunoir first stated the existence of a circular sphincter and a radial dilator. This view was supported by Valentin (1837), Krohn (1837), Bruch, Brücke, Köl liker, Henle, Luschka, Merkel, v. Hüttenbrenner, Faber, Dogiel, Hulke, Iwanoff, Jeropheeff, and others. It was controverted on the anatomical side by Arnold, Hall, Hampeln, v. Michel, Schwalbe, Koganei, Fuchs, Eversbusch, Retzius, and others. The present state of the question is that the anterior layer of retinal pigment epithelium acts as a dilator muscle (Juler, L. Müller, Gabriélidès, Grunert). On bleaching, the cells of this layer resemble in all respects unstriated muscle fibres. They stain in the same manner, and may be well demonstrated, for example, with Mallory's phosphotungstic acid hæmatoxylin after hardening in Zenker's fluid (Verhoeff). Further, Szili has brought forward evidence to show that the sphincter pupillæ is also derived from the retinal epiblast. These muscles would, therefore, resemble the arectores pilorum of the skin in being formed from epiblast.

The physiological evidence in favour of a distinct dilator contractile tissue in the iris is stronger than the histological, the researches of Langley and Anderson being quite conclusive. Historically it is inextricably mixed up with the vaso-motor theory, so the two are best considered together.

In 1840, Crimelli showed that injection of coloured oil into young eyes (children) caused constriction of the pupil; and Rouget (1866) proved the same fact by injecting fluid into the ophthalmic artery. The early literature will be found in the papers of Zeglin ski and Heese.

Grünhagen, in a series of papers from 1864 to 1893,

warmly supported the vaso-motor theory, whereby a diminished quantity of blood in the vessels leads to shrinkage of the iris. It is clear also that constriction of the arteries, accompanied by contraction of the longitudinal muscle fibres in their walls, may lead to dilatation of the iris by dragging the sphincter outwards (Langley and Anderson). Budge and Waller (1851) and Budge (1855) proved that dilatation through the sympathetic can occur in the absence of variations of blood supply, *e.g.*, after death. Waller (1856) showed that making the iris of a white rat bloodless by pressing upon the eye had no effect upon the pupil. Brown-Séguard (1859) found barely appreciable constriction of the pupil on injecting blood into the ophthalmic artery, though the effect is greater a day or two after death (Mosso, 1874). François-Franck (1880) obtained dilatation through the sympathetic after bleeding the animal to death.

Claude Bernard (1852), and Waller (1853) demonstrated vaso-motor nerves to the ears, etc., and Kuyper (1859) to the iris, in the cervical sympathetic. Salkowski (1867) also proved that constriction of the vessels accompanied dilatation of the pupil, Donders noting the same fact in albino rabbits, and Becker in human albinos. Sinitzin showed that excision of the superior cervical ganglion was followed by dilatation of the vessels. Arlt, Jr. (1869) and François-Franck (1880) proved that dilatation of the iris and constriction of the vessels of the ear do not occur synchronously. Langley and Anderson (1892) proved the same fact for the iris vessels, showing at the same time that no deductions can be made as to time relations from the vessels of the ear.

There is evidence that the vaso-motor and pupillo-dilator fibres run independent paths. Bernard (1862) found in the dog that section of the first and second thoracic nerves caused dilatation of the pupil, but no vascular change in the skin of the head, whereas section of the thoracic sympathetic between the second and third ribs caused the reverse effects. Langley and Anderson (1892) showed that dilatation of the

pupils and distinct constriction of the vessels of the iris were caused by the first three thoracic nerves, and by these only; but the readiness and extent of the pupillary dilatation was not proportional with the several nerves, to the readiness and extent of the arterial constriction. Schiff (1872) showed that the two sets of fibres could occasionally be isolated as separate bundles in the cervical sympathetic, and one or other effect obtained alone. Budge and Waller (1851) found that the pupillo-dilator fibres, after leaving the superior cervical ganglion, accompanied the internal carotid artery in its canal, running to the Gasserian ganglion; whilst François-Franck (1880) showed that the superior cervical ganglion gives off two strands to the carotid canal, and the external causes dilatation of the pupil, but no increase in pressure in the peripheral end of the carotid, the other strand causing the reverse effects. François-Franck also found separation of the two tracts in the annulus of Vieussens, but these experiments are inconclusive (Langley and Anderson). Some of the short ciliary nerves cause constriction, others dilatation of the pupil, according to François-Franck, whilst neither cause variation of the retinal vessels or change in intra-ocular pressure. These experiments are also inconclusive. Jegorow (1886) found that after section of the long ciliary nerves, stimulation of the central end of the vago-sympathetic causes strong contraction of the retinal vessels, but no pupillo-dilatation, whilst stimulation of the peripheral end of a long ciliary nerve causes the reverse effect.

Waller (1856) and Vulpian (1873) noticed in the white rat that no constriction of the iridic vessels accompanies dilatation of the pupil by atropin. Langley and Dickinson (1890) showed that intravenous injection of brucin may eliminate pupillo-dilatation from the sympathetic, the vasoconstriction of the vessels of the ear still remaining, and Langley and Anderson (1892), by the same method, were able to obtain complete constriction of the vessels of the iris without any change in the size of the pupil.

Even if the relative unimportance of the vaso-motor changes be conceded, the dilatation of the pupil may be due to inhibition of the sphincter pupillæ. This possibility was announced by Grünhagen and Samkow (1875), without further investigation, except that they showed that the tone of the sphincter can be diminished by direct stimulation, the muscle becoming elongated. François-Franck (1880) expressed the same view with some reserve, whilst Gaskell (1886), influenced largely by dubious analogies, definitely advanced the inhibitory theory. Kölliker (1855) had already obtained dilatation after removal of the sphincter, but the conditions of the experiment prevent its being accepted as positive evidence. The inhibition of antagonists on stimulation of muscles is definitely proved in many cases, and inhibition of the sphincter tone is also proved, but whether the cervical sympathetic has this property must still be considered *sub judice*, though with distinct bias to the negative. In any case it would afford no disproof of the existence of a dilator muscle.

The possibility of pupillo-dilatation as the result of relaxation of the ciliary muscle was advanced and controverted by Langley and Anderson (1892).

Most important are the experiments which definitely prove the existence of a contractile dilator mechanism. Weber first showed that stimulation of the sclerotic near the limbus caused dilatation of the pupil, whilst stimulation of the cornea was followed by constriction of the pupil. Bernstein and Dogiel (1865-67) found that the result might be varied by other arrangements of the electrodes (see Langley and Anderson (1892)); their experiments were confirmed by Engelhardt (1869).

Local dilatation can be obtained by other means. Hensen and Völkers (1868) found it on stimulating a single ciliary nerve, but this may be followed by general dilatation or general constriction (François-Franck). Jegorow (1886) obtained local dilatation in the dog from stimulation of a single long ciliary nerve; on section of all but one ciliary

nerve, subsequent excitation of the cervical sympathetic or of a sensory nerve causes well-marked local dilatation.

The effects of stimulation of the sclerotic near the cornea have been exhaustively investigated by Langley and Anderson (1892). They obtained: (1) Movement of the iris on the side opposite to local dilatation, which was of such a nature that it could not be explained by inhibition of the sphincter in the presence of radial elastic fibres; (2) local dilatation of the pupil with simultaneous local contraction of the sphincter; (3) contraction of a radial strip of the iris. They also proved the absence of any great elasticity in the iris, such as might account for some of the results on the theory of sphincter inhibition.

THE EFFERENT PUPILLO-CONSTRUCTOR PATH. *The Third Nerve.*—Romberg (1851), in his text-book on "Nervous Diseases," refers to dilatation of the pupil as a symptom of paralysis of the third nerve. Budge (1851) states that constriction of the pupil follows stimulation of the third nerve in recently killed animals and man; this observation was confirmed by v. Trautvetter (1866). Schiff (1868) thought that the iris fibres were on the inner side of the trunk of the nerve, since section of the inner fibres caused paralysis of the iris movements without abrogating the movements of the globe. Hensen and Völkers (1868) found pupil constriction from stimulation of the ciliary ganglion and the short ciliary nerves; excitation of single short ciliary nerves caused local constriction, whilst section caused local dilatation. Adamük (1870) confirmed the importance of the ciliary ganglion: he further stimulated the origin of the third nerve in the floor of the aqueduct of Sylvius, and adduced evidence to the effect that the pupillary fibres passed backwards from the nucleus on their way to the trunk of the nerve. Hensen and Völkers (1878) proved that the fibres pass forwards rather than backwards, Adamük's results being due probably to stimulation of afferent fibres running forwards in the medulla to join the centre.

This course for the pupillo-constrictor fibres has been confirmed by all subsequent observers, the only discovery of importance being that there is a cell station in the ciliary ganglion. This was proved by Langley and Anderson (1892), both by the nicotin method and by the degeneration method. If the third nerve is cut within the skull, many degenerated fibres are found running to the ganglion, but none peripherally of it (Apolant, 1896). The preganglionic fibres running from the third nerve to the ciliary ganglion are mostly small medullated fibres. The postganglionic fibres running in the short ciliary nerves are three or four times as numerous as the preganglionic ones, and also consist chiefly of small medullated fibres. These facts were stated by Bidder and Volkmann (1842). These autonomic (Langley) postganglionic fibres differ, therefore, from the rule which applies, though with many exceptions, to the postganglionic fibres of the sympathetic system in being medullated.

Further proof of the origin of the postganglionic pupillo-constrictor fibres in the cells of the ciliary ganglion is afforded by the Nissl method. This method is extremely delicate, but demands the greatest care in the interpretation of the results. In this case it gives valuable confirmatory evidence; in others the conclusions deduced from it must be accepted with reserve. There is even considerable divergence of opinion in the results of experiments upon the ciliary ganglion. Thus Bach (1899) found that nearly all the cells were degenerated after excision of the iris and ciliary body; none when the cornea was removed. Marina (1899-1901) found degeneration from destruction of the cornea, but much more after iridectomy. Bumm (1902) counted the cells and found the normal average to be 6432. After cutting the ciliary nerves, 3854 remained unaffected; after excising the superior cervical ganglion, the cells were reduced to 2587. The latter result may be due to the removal of afferent impulses (*cf.* Warrington).

Paradoxical Pupillo - Constriction. — Under ordinary

conditions the pupillo-constrictor centre emits tonic impulses, so that when these are cut off by section of the constrictor path in any position the pupil becomes slightly larger than normal. It has occasionally been observed that the pupil is smaller than normal; this is called paradoxical pupillo-constriction. It has been less frequently seen than paradoxical pupillo-dilatation, to which reference will be made later.

Paradoxical pupillo-constriction has been investigated by Anderson (1902), only an abstract of his results having been as yet published. He found that after excision of the left ciliary ganglion and section of the right third nerve proximally of the ganglion in a kitten, the two pupils were equally dilated until regeneration occurred on the right side 8 days later. In a cat the right pupil continued to be widely dilated 38 days after division of the right short ciliary nerves. Under certain circumstances, however, the pupil on the side of the excision was smaller, *e.g.*, in the cat the right pupil was smaller in dim light than the left after local application of eserine to both eyes in equal quantity; and 18 days later the right pupil was smaller after the death of the cat.

In another cat the left pupil immediately after excision of the left ciliary ganglion was very widely dilated, but next day the left pupil had become slightly smaller, and was smaller than the right in dim light if the cat became restless under observation. On the same day after administration of ether and section of both cervical sympathetic nerves the left pupil became a slit, though the right was almost maximally dilated, and for 48 hours after death the left pupil remained much smaller than the right.

In other observations made 2 and 318 days after denervation of the sphincter on one side, the pupil on the side of the lesion was smaller after the death of the animal, though previously it had been the larger since the denervation.

Anderson concludes that the paradoxical pupillo-

constriction is due to increased excitability of the denervated sphincter, the exciting stimuli in the observations mentioned being alterations in the blood supply, eserin, and probably ether (see, however, the observations on paradoxical pupillo-dilatation).

THE EFFERENT PUPILLO-DILATOR PATH.—Investigations on the pupillo-dilator path have been attended with more ambiguous results than those on the constrictor path.

The Cervical Sympathetic Nerve.—Parfour du Petit (1727) first showed that section of the cervical sympathetic was followed by constriction of the pupil upon the same side, as well as by other symptoms which do not concern us here. The observation was confirmed by Molinelli (1755), Arnold, Stilling and others. Valentin pointed out that section caused a short and transitory dilatation of the pupil, followed by constriction which remained permanent. Serafino Biffi (1846) repeated Petit's experiments and confirmed them, and further supplemented them by showing that stimulation of the sympathetic causes dilatation. Reid (1848) isolated the sympathetic from the vagus fibres in the cat, and showed that only the sympathetic caused dilatation of the pupil on stimulating the peripheral end.

Budge (1851-55) first seriously attacked the problem of the innervation of the pupil, and it is only within the last few years that anything of importance has been added to his results, though they have been corrected in details. He found that if the spinal cord between the sixth cervical and the fourth thoracic vertebræ is isolated by transverse section above and below, then stimulation of this area causes dilatation of both pupils, which is abrogated on one side if the corresponding sympathetic is cut. Stimulation of the cord above or below this region caused no effect. Hence Budge concluded that there was a centre for the dilatation of the pupil here; he called it the *centrum cilio-spinale inferius*. He also traced the dilator fibres from this centre to the cervical sympathetic, showing that they leave the cord by the anterior roots of the seventh and eighth cervical

and first and second thoracic nerves; Budge also described a *centrum cilio-spinale superius*, which he thought was in the region of the nucleus of the hypoglossal nerve. He thought that the superior cervical ganglion received pupillo-dilator fibres directly from this centre as well as from the inferior one through the sympathetic. The experiments upon which the idea was founded are open to another interpretation, and afford no evidence of a superior centre. Schiff (1855) confirmed Budge's results, but opposed his idea that the *centrum cilio-spinale inferius* was an automatic and independent centre. He gave good evidence to show that it was under the control of impulses descending from above, so that hemisection of the cord above the fourth cervical vertebræ caused constriction of the pupil on the same side, and the other effects of cutting the sympathetic. He therefore considered that the superior centre alone was automatic.

The complete demonstration of the dilator path was intimately bound up with the discovery and investigation of the sensory pupillary reflex, which must, therefore, be referred to in this connection. Chauveau (1861) discovered that dilatation of the pupil followed excitation of the posterior columns of the cord; this only occurred with the intact cord in his experiments. (It had long been known that pupil dilatation often occurred in trigeminal neuralgia (Notta, 1854)). Claude Bernard (1862) first showed that excitation of the central end of any sensory nerve caused dilatation of the pupil; he found that the effect was abolished by section of the anterior roots, which are known to carry the pupillo-dilator fibres.

Balogh (1861) noticed dilatation during asphyxia, even if the superior cervical ganglion had been removed. Stimulation of the trunk of the fifth nerve, or of the Gasserian ganglion, or of the ophthalmic division of the fifth, caused dilatation. If the trunk of the fifth nerve was cut, stimulation of the medulla caused no change in the pupil. He therefore arrived at the deduction that the fifth nucleus is the upper centre for the dilator fibres, and that the dilator

fibres all pass through the Gasserian ganglion and thence into the ophthalmic division of the fifth.

Oehl (1862) obtained dilatation of the pupil from the first division of the fifth after excision of the superior cervical ganglion; there were no dilator fibres in the trunk of the fifth nerve. Hence he concluded that the dilators arise in the Gasserian ganglion—an erroneous deduction. Guttman (1864) supported this view; he opposed the medullary centre and found slight pupillo-constriction after dividing the fifth just proximal to the Gasserian ganglion.

Salkowski (1867) confirmed Budge's experiments and supported the view of the medullary centre, which he found to be the reflex centre for the sensory stimuli. He asseverated the existence of a single pupillo-dilator path from the medulla through the centrum cilio-spinale inferius to the cervical sympathetic.

Nawalichin (1869) confirmed Balogh's results and fell into several errors. He found that the sensory reflex was eliminated by section of the cord above the spinal centre of Budge, and also that the sympathetic is not the only dilator tract. The latter view was founded upon two chief observations: (1) if the cord is cut at the level of the third cervical vertebra, stimulation of the upper cut end causes dilatation; (2) if the cord is cut below the medulla, asphyxia still causes pupillo-dilatation. Both of these observations are correct, but they are open to other interpretation. Vulpian (1874) also thought that the trunk of the fifth nerve contained dilator fibres, both from his experiments in which it was cut, and also because the sensory reflex from the sciatic nerve persisted after extirpation of the superior cervical and stellate ganglia.

Hurwitz (1878) repeated Vulpian's experiments, and performed two new ones which are of some importance. If the superior cervical ganglion was removed, then after at least 120 hours' interval it is found that direct stimulation of the iris of the atropinised eye of a curarised animal causes not the slightest trace of dilatation. If the sympathetic is cut

a few days before stimulation of a sensory nerve, pupillo-dilatation is not abolished, but is slower in onset and more prolonged.

Schiff and Foa (1874) devoted special attention to the sensory reflex, and found that the pupil may be regarded as an æsthesiometer. They confirmed Chauveau's result that the afferent path runs in the posterior columns of the cord, adding also the grey matter; they obtained no sensory reflex after section above or below the medulla.

François-Franck (1878-80) made an exhaustive investigation of the whole subject. The results which concern us here are as follow. From the fact that section of the trunk of the fifth nerve is followed by constriction of the pupil, he concluded that that nerve contains dilator fibres. He also found dilator fibres in the vertebral nerve. He showed that the dilators pass by the rami communicantes of the fourth cervical to the sixth or seventh thoracic in cuts to the thoracic sympathetic. Thence they pass into the stellate ganglion, and from there, by the anterior limb of the annulus of Vieussens, to the cervical sympathetic. He found no pupillo-dilators in the posterior limb of the annulus, but this is untrue (Langley and Anderson). The sympathetic receives no other dilator fibres in the neck. All the ciliary nerves are pupillo-constrictors with the exception of two or three. The short ciliaries cause rapid constriction, whilst the long ciliaries cause slow dilatation. Extirpation of the stellate, or of the superior cervical ganglion, causes greater dilatation of the pupil than simple section of the sympathetic nerve; hence he concludes that these ganglia exert a tonic influence over the irido-dilator mechanism. Guillebeau and Luchsinger (1880) ascribed the dilatation from the vertebral nerve to sensory fibres contained in it.

Luchsinger (1880) supported the view that the inferior cilio-spinal centre is automatic. He obtained the sensory reflex after section of the cord, if the excitability is increased by picrotoxin or strychnin. Tuwim (1881) failed to obtain dilatation from sensory stimuli after cutting the cord. He

confirmed the discovery of François-Franck that the superior cervical ganglion exerts a tonic influence; he found the pupil smaller on the side in which the ganglion was extirpated than on the side in which the sympathetic was cut. Guillebeau and Luchsinger (1882) obtained the sensory reflex in young cats after section of the cord without artificially increasing the excitability of the cord, and this result was also found in cats by Ott (1882).

Shegliniski (1885) showed that the pupillo-dilators in birds run in the first division of the fifth. They do not run in the cervical sympathetic. This statement was controverted by Grünhagen, but has been substantiated by Langley (1903). It was also confirmed by Jegorow (1886), who found vaso-motor fibres in the sympathetic, but no pupillo-dilators. This observer also confirmed the course of the dilators in mammals in the ophthalmic division of the fifth, and in the long ciliary nerves.

Bellarminow (1886) first used the photographic method for recording the pupillary movements. He distinguishes between (1) direct (sympathetic) dilation and (2) reflex dilation. The latter occurs whether the sympathetic is intact or not. He found that the pupil varies independently of the blood pressure or the intraocular pressure.

Katharina Schipilow (1886) traced the dilators in the frog. She found no difference between cutting the sympathetic and excising the sympathetic ganglia.

Nawrocki and Przybylski (1891) found that in cats the dilators leave the cord by the ventral roots of the eighth cervical and first and second thoracic nerves. The fibres do not pass through the ciliary ganglion, but enter the long ciliary nerves. These authors also admit a cranial dilator path, though they deny the presence of dilators in the vertebral nerve. There is a centre in the brain, but there are no sufficient grounds for supposing that there is an inferior cilio-spinal centre.

Braunstein (1894) re-investigated the whole subject in an extremely careful research, using Bellarminow's photo-

graphic method. He found the dilator fibres in the rami communicantes of the seventh and eighth cervical and first and second thoracic nerves of the cat. He found no dilators in the posterior limb of the annulus of Vieussens. Above the superior cervical ganglion the dilators run in a special branch, separate from the carotid branches, to the Gasserian ganglion. Stimulation of a long ciliary nerve caused partial dilatation (as opposed to general dilatation found by François-Frank and Bellarminow).

The pupillo-dilator fibres in the cervical sympathetic end around the cells in the superior cervical ganglion. This has been proved by the degeneration method by Waller and Budge (1851-53), and by the nicotin method by Langley and Dickinson (1899-1900).

Langley (1892, sqq.) found the dilator fibres in the first three thoracic nerves. In the cat and dog the third has much less effect than the other two; in the rabbit, and apparently in the ape, the third may have a greater effect than the first, but never so great an effect as the second. It has already been mentioned that Langley and Anderson (1892) found dilator fibres in the posterior limb of the annulus of Vieussens, as well as in the anterior limb, though they were not so numerous.

The preganglionic fibres of the cervical sympathetic, including, therefore, the pupillo-dilator fibres, consist of fine medullated fibres. The postganglionic fibres in the branches from the superior cervical ganglion consist for the most part of non-medullated fibres. Degeneration of these fibres has been specially investigated by Tuckett (1896).

By the Nissl method, according to Marina, some of the cells of the superior cervical ganglion degenerate when the ciliary nerves are cut.

The Fifth Nerve.—We have already seen that several observers considered that there were pupillo-dilator fibres in the fifth nerve. Magendie (1824) first proved that section of the fifth within the skull in the rabbit caused constriction of the pupil. This was denied by Longet

(1842). Valentin and Claude Bernard showed that the effect was transitory, whilst the effect of section of the ophthalmic division of the fifth was lasting. Balogh, Nawalichin, Vulpian, and François-Franck all confirmed the presence of dilators in the trunk of the fifth. Schiff (1867) thought they were sympathetic fibres from the cavum tympani. Rembold (1880) agreed with Schiff that the tone of the dilator was kept up by afferent sensory stimuli, explaining thereby the miosis which follows section of the fifth. In order to explain the constriction caused, according to several authors, by excitation of the trunk of the fifth, he considered it probable that there were actually pupillo-constrictor fibres in the fifth nerve. Eckhard (1892) also thinks that there are constrictors in the fifth.

It is unnecessary to enumerate all the authors who consider that there are dilators or constrictors in the trigeminal. Braunstein and Hurwitz may be held to have proved their absence. Further, Langley could not obtain local dilatation of the pupil from stimulation of the sclerotic after excision of the superior cervical ganglion some time before, and Anderson failed to obtain it even on stimulating the iris under the same conditions. Other observers, amongst them myself, have failed to obtain any movement of the pupil after section of the third nerve and the cervical sympathetic. It may, therefore, be considered definitely proved that all the dilator fibres run in the cervical sympathetic.

Paradoxical Pupillo-Dilatation.—Paradoxical pupillo-dilatation is the antithesis of paradoxical pupillo-constriction. "Section of the cervical sympathetic causes constriction of the pupil, and simultaneous removal of the superior cervical ganglion on the other side causes slightly greater constriction, as first shown by Budge, but in certain circumstances the pupil on the side without the ganglion becomes larger than the pupil on the side with the nerve alone cut. This greater dilatation on the more paralysed side has been called paradoxical pupil-dilatation by Langendorff. Moreover, if only a superior cervical ganglion be excised, the pupil on the

paralysed side may nevertheless become larger in certain circumstances than the normal pupil. This is also spoken of as paradoxical dilatation." (Anderson.)

Budge (1855) first called attention to the occurrence of paradoxical pupillo-dilatation. After section of the left sympathetic and of the branches above the right superior cervical ganglion in a young rabbit he found the right pupil smaller than the left $\frac{1}{2}$ hour later, equal after 24 hours, and the right larger than the left after 48 hours. Schiff (1868) observed the effect after section of the sympathetic, and after excision of the ganglion; he connected the phenomenon with oxygenation of the blood after previous asphyxiation. Surminski (1869) and Tuwim (1881) observed it after atropin. Kowalewski (1886) saw it in a kitten after the administration of chloroform. Braunstein (1894) observed it after curare; and Tuckett (1896) incidentally in the course of another research. Langendorff (1900) investigated the subject specially, and noticed the phenomenon after anæsthetics and after death. Lewandowski (1900) also called attention to these paradoxical effects, and showed that they could be produced by dyspnœa. It was also observed incidentally by Langley (1901) and Levinsohn (1902).

The subject has been exhaustively investigated recently by Anderson (1903). He proved that the effect might be observed as soon as 1 day after the lesion, and as long as more than a year. Excitement, dyspnœa, anæsthesia, death, are conditions which evoke the effect. It is produced much more readily by slight dyspnœa in kittens than in cats. The paradoxical effect persists even when the postganglionic branches of the ganglion have been allowed to regenerate. Immediately after removal of the ganglion on one side, and section of the sympathetic on the other, there is always greater paralysis on the side without the ganglion. Later there is frequently greater paralysis on the side with the nerve cut, but if sufficient care is taken to insure a quiet condition of the cat, the signs of greater paralysis are often transferred to the side without the ganglion.

In the quiet condition of the cat the evidence is therefore often against the views (1) that the sphincter is weakened on the side without the ganglion (Budge, Tuwim, Levinsohn), or (2) that there is permanent contracture of the vessels of the iris, or dilatation on this side (Surminski, Langendorff), or (3) that on the side with the ganglion the dilator is inhibited (Kowalewski).

After the local application of eserine to the eyes of a kitten the pupil is smaller on the side from which the superior cervical ganglion has been removed so long as the kitten is quiet, but slight dyspnoea will cause the pupil to become almost maximal though the normal control pupil is very small. A similar result may be obtained when the sphincters are contracting strongly in bright light instead of under the influence of eserine.

This paradoxical pupillo-dilatation must therefore result from an actual increase of tone in the dilator on the side without the ganglion. This increase of tone may be directly demonstrated in the nictitating membrane and lids. The paradoxical effect is therefore due to an increased excitability of the contractile tissues on the side without the ganglion (Lewandowski, Anderson).

The great accentuation of the paradoxical effect seen under anaesthesia does not occur until dyspnoea arises. If only the sympathetic has been cut, the paradoxical effects occur much later, and are much less pronounced.

The paradoxical effects show that the ganglion cannot inhibit the automatic excitability of the contractile tissues with which it is still in connection.

Bright light cannot inhibit the paradoxical dilatation through the third nerve, since the effect will still persist in bright sunlight for more than a minute.

Inhibition of Antagonists.—It is known that in the case of the skeletal muscles contraction of a given group is accompanied by simultaneous active relaxation of the antagonistic group (Sherrington). By analogy, therefore, it is not improbable that constriction of the pupil through the

third nerve should be accompanied by simultaneous active inhibition of the dilator, also carried out through the third nerve by means of inhibitory dilator fibres. And, indeed, Waymouth Reid (1895), from consideration of the electrical phenomena occurring during contraction of the sphincter, concluded that this actually happened. Anderson (1903), however, has brought forward strong arguments against this view. Thus, using bright light as a stimulus to contraction of the sphincter, it is found that the paradoxical dilatation may arise and continue for more than a minute in bright sunlight; and further, under the same conditions, a difference between the two pupils caused by paralysis of one dilator is not diminished, but increased by brighter illumination of the eyes. Neither of these observations is consistent with inhibition of the sphincter through the third nerve.

The iris is not under the control of the will, hence these motor nerves are invariably set in action indirectly, either by reflex stimuli, or by what I shall call *synkinesis*, i.e., association with other voluntary or involuntary movements.* There are two chief reflexes, and two chief synkineses or associated movements. (1) The Light Reflex; (2) The Accommodation Synkinesis; (3) The Sensory Reflex; (4) The Cerebral Synkinesis.

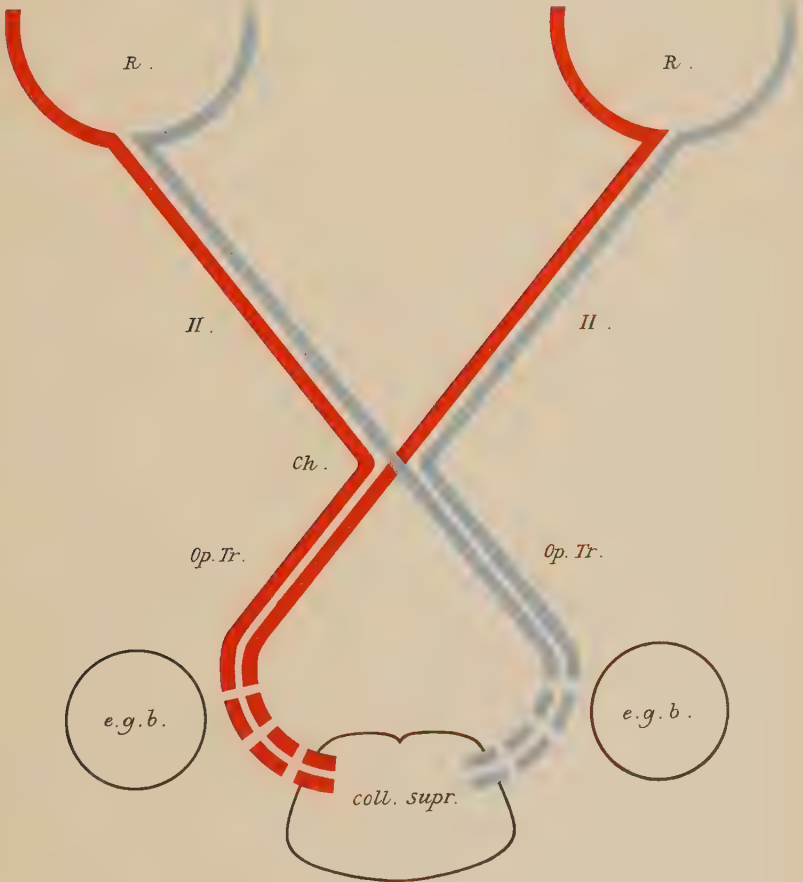
THE LIGHT REFLEX is carried out entirely through the mechanism of the constrictor centre. Of the afferent paths we know very little for certain. The fibres are contained in the optic nerve, and they arise from all parts of the retina. The optic nerve contains large and small fibres; it is possible that the large fibres are concerned with visual sensations, and that some of the fine ones are afferent pupillo-constrictor fibres. The opposite view has also been advanced. It is certain that the pupillary fibres undergo partial decussation

* The corresponding term for the association of ideas, or an associated idea, would obviously be *synpsychosis*.

PLATE II.

THE AFFERENT PUPILLO-CONSTRUCTOR PATH.

R., retinæ; *II*, optic nerves; *Ch.*, chiasma; *Op. Tr.*, optic tracts; *e.g.b.*, external geniculate bodies; *coll. supr.*, superior colliculus or anterior quadrigeminal body.



in the chiasma, and enter the optic tracts. It is also certain that they do not enter the lateral geniculate body, but leave the tract to pass by a path which is as yet conjectural to the third nucleus. The tone of the constrictor centre is kept up by constant afferent impulses along this tract; it is possible that it also possesses inherent tone. The tone is probably continually depressed by less effectual impulses along the fifth and other sensory nerves.

There are two types of light reflex, viz., that through the retina of the same side, or the direct reflex, and that through the retina of the opposite side, or the consensual reflex; *i.e.*, light falling upon the retina causes constriction of the pupil—a direct reflex, but it also causes constriction of the opposite pupil—a consensual reflex.

Lambert (1760) found that the constriction increased with the area of the retina which was stimulated. E. H. Weber (1851) found that it was stronger the nearer the affected part lay to the macula, and was strongest of all when the luminous body was the object of fixation.

Herbert Mayo first obtained constriction of the pupil from experimental stimulation of the optic nerve. Flourens (1824) placed the reflex centre in the corpora quadrigemina, a view concurred with by Longet, Budge, and others. Knoll (1869) showed that the whole anterior colliculus might be destroyed without preventing the light reflex. This was confirmed by v. Bechterew (1884) and others—recently by Ferrier and Turner (1901).

The Afferent Pupillo-Constrictor Path (Plate II).—The fact that, like the afferent visual fibres, the afferent pupillo-constrictor fibres undergo partial decussation in the chiasma is proved by the hemiopic pupil reaction of Wernicke. This observer found that any lesion which destroyed one optic tract caused loss of the light reflex on stimulation of the corresponding halves of both retinae, whilst stimulation of the opposite halves gave the normal reaction. Attention was called to the fact that the pupillary and visual paths are not identical by the effects of destruction of the superior

colliculi, and this was confirmed by the effects of destruction of the lateral geniculate body. I have in the first lecture given additional evidence that the visual fibres divide, probably more frequently than has hitherto been supposed. It is not improbable that the pupillary reflex is carried out by means of collaterals.

In any case, destruction of the lateral geniculate body does not abolish the light reflex (v. Bechterew, Henschen and others). Hence the pupillary fibres leave the tract before it reaches the geniculate body. Bogroff and Flechsig (1886) describe a tract passing directly into the stratum griseum centrale of the third ventricle. According to an earlier view of v. Bechterew (1883), the fibres do not enter the optic tract, but pass into the grey matter of the third ventricle close behind the chiasma. Such a view is negated by the Wernicke reaction, and has apparently been abandoned by v. Bechterew (1900); he now thinks they leave the optic tract at the level between the corpus cinereum and the root fibres of the third nerve, *i.e.*, near the entrance of the optic tract into the geniculate body, running thence to the posterior part of the third ventricle, where they make connections with cells which send axones to the third nucleus of the same side.

Darkschewitsch (1886) thinks that the pupillary fibres leave the optic tract near the geniculate body and pass through the thalamus to the ganglion habenulæ. Thence fresh fibres pass through the posterior commissure to his obere Oculomotoriuskern. This, however, has been shown by v. Bechterew and others to have nothing to do with the third nerve. His results have been supported on comparative anatomical grounds by Bellonci, and also by Mendel.

The evidence is in favour of the afferent pupillo-constrictor fibres making new connections before reaching the third nucleus. Bernheimer (1899), however, thinks that they pass direct to the third nucleus, but Bach (1900) was unable to confirm his results. It must be admitted that the question is by no means settled. It seems most likely that

the fibres pass through the superior brachium into the superior colliculus, there making new connections with cells which convey the impulses to the third nucleus of the same and also of the opposite side. This view is held by Barker, and is probable from the histological researches of Held. It would account satisfactorily for all the facts, including both the consensual reaction and the hemiopic pupil reaction. The effects of extirpation of the superior colliculus are not necessarily fatal to this theory. It is most probable that the afferent pupillary fibres end in the lateral part of the colliculus, and this may quite easily have escaped destruction in experiments in which it is so important that the lesion should be strictly localised.

The Pupillo-Constrictor Centre.—I do not intend to attempt in this lecture to unravel the tangle of speculations as to the reflex pupillary centres. The number of these centres which have been described and localised by various writers, each with the utmost assurance, is bewildering in the extreme. To name only a few, we have several constrictor centres, several dilator centres, not to mention various cortical and sub-cortical centres of each kind, and finally Bach has added to the confusion by hypothecating an inhibitory constrictor, and even in his last paper an inhibitory dilator centre. The explanation is to be found in wild theorising upon quite inadequate data, and much of this is due to the use of the unfortunate term "centre." One is inclined to wish that this term might be abolished from neurology, so great is the ambiguity and confusion to which it has given rise. The intercommunications between the cells of the central nervous system are so complex that there are almost innumerable alternative paths whereby any given group of efferent cells may receive excitatory impulses. Our aim should be, first to determine the efferent cells governing any given movement, second to determine as far as is possible which are the afferent tracts which can lead directly or indirectly to those cells, and third to find out *how* each of those afferent tracts leads to the efferent cells. The last

problem is the most difficult, and we shall find that many of the afferent tracts are very devious, and have many cell-stations on their way. Each of these may be dignified with the title "centre," or better, none of them.

There are one or two points, however, which must be mentioned in spite of the obscurity of the subject. We have seen that the third nerve contains all the constrictor fibres for the iris. We have reason to believe that the light reflex is an active constrictor effect and not an inhibitory dilator effect; for, seeing that probably both centres exert a tonic influence, it is obvious that the result might arise from either of these causes. If this reasoning is sound, the only true centre for the light reflex is the part of the nucleus of the third nerve which gives rise to the pupillo-constrictor fibres. Most authors are inclined to agree that this is the Edinger-Westphal nucleus, which consists of small cells occupying the median part of the third nucleus. It may be subdivided into two parts, an anterior paired nucleus and a posterior unpaired nucleus. The former, according to Bernheimer, contains the pupillo-constrictor cells.

This view is not universally adopted, and there are still some—chiefly neuro-pathologists (*e.g.*, Sacki and Schmaus, Schaffer), who adhere to the inhibitory dilator theory, or a modified form of it. Argyll Robertson (1869) must be considered principally responsible for this view, which he held best explained the pupil phenomenon which bears his name. Pathological evidence in favour of it has been collected by Wolff (1899), and it has received some support from the (inconclusive) experiments of Bach, Ruge and others.

Marina (1901-3) thinks that the ciliary ganglion is the centre for the light reflex, and he brings forward some ingenious experiments to prove his point. They cannot, however, be considered conclusive.

Very conclusive evidence in favour of the supreme importance of the third nucleus in the light reflex is afforded by the fact that variations in illumination have no effect on the pupil after section of the third nerve (Braunstein and others).

Anderson (1903) points out the necessity for care in eliminating all tactile and other sensory reflexes in these experiments. They prove that the light reflex is entirely through the pupillo-constrictor mechanism, and that inhibition of the dilator tone plays no part. This is additional evidence that the sphincter and dilator do not follow the law of contraction and relaxation of antagonists (see p. 46).

THE ACCOMMODATION SYNKINESIS is a constrictor effect commonly associated with accommodation. It is more nearly related, however, to the convergence which normally synchronises with accommodation, since it is possible to accommodate without inducing constriction of the pupil, whereas this invariably occurs during convergence. Very little is known about this phenomenon; even the views stated are open to doubt, but there can be no doubt that it is not a true reflex, but a case of associated movement. The same remark applies to the well-known lid-closing phenomenon.

The accommodation synkinesis has been known since Scheiner (1619). The efferent fibres for accommodation were investigated by v. Trautvetter (1866), Hensen and Völkers (1868, 1878), Kaiser (1868), Adamük and Woinow (1871), and others. Adamük and Woinow found that the pupillo-constriction was not proportional to the distance of the point of fixation. Olbers (1780), on the other hand, had already shown that it was proportional to the angle of convergence, and E. H. Weber (1851) proved that constriction of the pupil occurred on convergence without accommodation, but not on accommodation without convergence; this can be shown by the use of prisms. Hering (1868) devised an experiment for showing that constriction of the pupil also occurs on accommodation without convergence, but Verwoort (1899) thinks that this was due to imperfect exclusion of convergence.

Adamük (1870) obtained depression of the eyes, strong convergence, and pupillo-constriction on stimulating the posterior part of the anterior colliculus in dogs and cats,

similarly convergence and pupillo-constriction from the floor of the aqueduct. These results were confirmed by Hensen and Völkers (1878), and the intimate association of the pupillo-constriction with the internal rectus was further demonstrated.

Henke (1860) put forward the view that the reverse effect, relaxation of accommodation for distance, was accompanied by active dilatation through the sympathetic. However this may be, Hensen and Völkers found that stimulation of the slightly more lateral sixth nucleus was accompanied by some pupillo-dilatation. This is probably an active pupillo-dilator *divergence synkinesis*.

Curious cases are on record in which pupillo-constriction accompanied outward movements of the eye (Adamük, Weiss, Sichel, v. Graefe, Schiff).

THE SENSORY REFLEX is a dilator reflex induced by tactile, pathic and other sensory stimuli. It is a complex effect exhibiting a primary rapid dilatation due to augmentation of the dilator tone through the cervical sympathetic, followed by a second dilatation, rapid in onset but very slow in its disappearance, due to inhibition of the constrictor tone. When originated through spinal sensory nerves, the afferent impulses are carried up in the posterior columns of the cord.

In dealing with the course of the pupillo-dilator path we have seen that Chauveau (1861) first obtained the sensory reflex experimentally by stimulating the posterior columns of the cord. He found that if the cord was cut above the inferior cilio-spinal centre the effect was abolished, except in one experiment on an ass, in which a very small effect was produced. Claude Bernard (1862) showed that the sensory reflex might be obtained on stimulation of the central end of any sensory nerve.

Reference has already been made in the same section to the work of Salkowski (1867), Balogh (1869), Hurwitz (1878), Schiff and Foa (1875), François-Franck, Luchsinger, Bellarminow, and Braunstein. Balogh (1861), however, was

the first to obtain the sensory reflex after section of the ordinary dilator path in his experiment after excision of the superior cervical ganglion. Hurwitz, as we have seen, found that the effect was very slow after the cervical sympathetic had been cut. Vulpian (1878) observed reflex dilatation after removal of both the superior cervical and stellate ganglia. v. Bechterew (1883) contended that the sensory reflex was entirely due to inhibition of the light reflex, *i.e.*, of the tonic action of the third centre. He based this view largely upon the findings of neuro-pathology, the light and pain reflexes being almost invariably abolished together. He also supported it by further experiments. Thus, if one optic nerve is cut, no further dilatation was caused in the eye of that side by pathic stimuli unless the opposite eye was open, and contraction thereby excited consensually in the sphincter on the side of the lesion. Secondly, the dilatation was inconsiderable when the eyes were examined in a dim light. Thirdly, the degree of dilatation did not exceed that which followed the withdrawal of the light. These experiments were confirmed by Mayer and Pribram (1884), and later by Braunstein (1894). The last-named author found that after section of the third nerve inside the skull, stimulation of the central end of the sciatic nerve with strong and weak currents at periods varying from 12 days to 7 months after the operation caused no reflex movements of the pupil. He observed no change in the size of the pupil between the operation and the final experiment, though during the latter he obtained dilatation from stimulation of the cervical sympathetic.

The subject has received attention from this point of view recently by Anderson (1903). As the result of five experiments in which the pupillo-constrictor tract was divided in some part of its course, he found that well-marked dilatation could be obtained by stimulating the sciatic nerve, pinching the skin, or stroking the hairs. The effect was accompanied by all the usual effects of exciting the cervical sympathetic, and all were abolished if this was cut in addition to the third nerve.

The converse aspect of the subject has also been disputed. Luchsinger (1880) and Guillebeau and Luchsinger (1882) obtained the sensory reflex after the cervical cord had been cut above the inferior cilio-spinal centre. Kowalewski (1886) failed to obtain this result, and similarly Braunstein. Anderson obtained a positive result in the only experiment specially directed to the point; the effect was slow, and was accompanied by slight retraction of the nictitating membrane and eyelids. Second stimulation was ineffectual unless an interval of some minutes was allowed to elapse. The effect continued after destruction of the brain and medulla, and hence cannot have been due to inhibition of constrictor tone.

Anderson considers that the ordinary sensory reflex is of two-fold origin:—(1) reflex augmentation of the dilator tone, causing relatively rapid and short dilatation; (2) reflex inhibition of the constrictor tone, causing a second rapid dilatation which only slowly and gradually subsides.

Hippus.—Anderson makes a valuable contribution to the obscure question of hippus. He found that this occurred not uncommonly after section of the third nerve, but ceased immediately on cutting the sympathetic. It was excited by tactile stimulation, or by a certain state of anæsthetisation. It might be accompanied by rhythmic movements of the eyelids and nictitating membrane.

THE CEREBRAL SYNKINESIS is also a complex phenomenon, and cannot be considered a simple reflex. It is induced by psychic stimuli, *e.g.*, fear, etc., and also by concentration of thought upon a bright light or a dark room. It is also largely an associated movement, accompanying eye movements which may be themselves due to sensory impulses.

The pure psychic reaction, entirely caused by ideas of light and shade, was described by Haab (1886), though Beer had long before discovered that he was himself able to alter the size of his pupils in this manner; it may account for some cases in which persons have apparently been able to alter their pupils at will. The phenomenon is unaccompanied

by any obvious movement of the eyes, and, therefore, cannot be called a synkinesis; it is, in fact, a *psycho-kinesis*. The reaction has recently been called in question by Bumke (1903), and it must be admitted that it is very difficult to exclude the many sources of error, of which accommodation is the most probable and difficult to avoid.

I propose now to discuss in detail my observations on the relationship of the cerebral cortex to the movements of the pupil.

Fontana, as long ago as 1770, showed that in the cat, even under the strongest light stimulus, the pupils dilated widely if the animal was frightened by a loud noise. A child's pupil can also be made to dilate, even during ophthalmoscopic examination of the macula, by a loud sound, such as clapping of the hands. Raehlmann and Witkowski consider that psychic impulses assist in maintaining the tone of the dilator centre, accounting for the constriction of the pupil during sleep by their absence.

Schiff and Foa (1869) first stimulated the cerebrum by electricity, and obtained dilatation of the pupils from stimulation of the anterior four-fifths, and of the cerebellum only by strong stimuli. They attributed the effect to the sensibility of the brain.

Hitzig (1871) sometimes obtained constriction of both pupils, but generally dilatation, rarely only one pupil reacted.

Similar experiments have been carried out by Bochart (1875), Danilewski (1876), Luciani and Tamburini, Grünhagen, Bessau, Ferrier, Horsley and Schäfer, Schäfer, Beevor and Horsley, Grünhagen and Cohn, Katschanowski, François-Franck and Pitres, Mislowski, Bechterew and Mislowski, and Braunstein. In most of these cases the observations were incidental during research directed to some other object. In all, dilatation was much more easily induced than constriction, and no accurate localisation was effected.

Most observers have regarded the effects as inconstant, and but little attention has been specially directed to them.

Thus Ferrier includes dilatation of the pupil with salivation from the submaxillary gland, changes in pulse and blood pressure, and "other indications of general reverberation throughout the organism." He regards them as "merely complications and not as results of localised cortical stimulation." On the other hand, Bechterew and Mislowski conclude that "stimulation of the given regions of the cortex and of the optic thalami has hit off the central endings (*Verlängerungen*) of the cervical sympathetic," and that "the chief reflex centre for the secretion of tears lies in the optic thalami, and that there, too, are found the central tracts of the cervical sympathetic, their prolongations (*Fortsetzungen*) being continued thence to the cortex." François-Franck is careful to distinguish between two causes of dilatation of the pupil resulting from cortical stimulation. One is a special and localised effect following excitation of definite foci in the cortex, and also obtained from excitation of the underlying fibres of the corona radiata and internal capsule. The other accompanies epileptoid convulsions resulting from stimulation of any and every part of the motor areas, and is never obtained from the underlying white matter, which does not induce the epileptic state. To the latter he attributes the dilatation after administration of curare which was observed by Bochfontaine. He perhaps lays too much stress upon this as a fundamental distinction, for it applies equally to other motor effects induced through the cortex.

My experiments were made principally upon cats; a few dogs and one monkey were also used. The animals were anæsthetised with ether, the degree of anæsthesia varying, but always being amply sufficient to cause insensitiveness to pain. The qualifying terms used apply to the condition of excitability of the motor areas of the cortex to stimuli of moderate severity, as shown by movements of the limbs of the contra-lateral side. "Epileptoid convulsions" is the term used to express the violent general movements which often follow stimulation of the motor area after exposure of

the brain to air, or prolonged or frequently repeated excitation. This condition is quite compatible with complete anæsthesia.

The cervical sympathetics were either cut or isolated on one or both sides. In the dog the vago-sympathetic was treated as a whole. This was also done in the cat to insure the complete division of all sympathetic fibres. In some experiments the superior cervical ganglion was extirpated to eliminate any dilator fibres which might reach the ganglion by any hitherto unknown course. Section of the sympathetic was usually followed by a distinct moderate constriction of the corresponding pupil, but this was certainly not invariably the case. Absence of a tonic dilator influence is probably under these circumstances due to the condition of anæsthesia of the animal.

I need not enter into further details of the operative procedures, which were those usually employed in cerebral physiology. It was important to keep the light falling upon the eyes as constant as possible throughout the experiment.

It is easy in the cat's eye to direct one's attention to the horizontal meridian. The constricted pupil being a vertical slit, the distance from the centre to the periphery can be divided into four imaginary parts, the pupil being said to be a quarter, a half, three-quarters, or fully dilated.

I have not paid much attention to any movements other than those of the eyes and pupils. Dilatation of the pupils is often obtained without any movement of the eyes or body. I have usually found that a slightly stronger stimulus is necessary to evoke it than that which is required to produce movement from excitation of the arm or leg areas; or the same strength of stimulus may suffice if the animal be slightly less under the influence of the anæsthetic.

(A) *Cat*.—In the cat dilatation of the pupil can be obtained from a considerable area in the neighbourhood of the crucial sulcus and from a considerable area of the occipital region. As the result of many experiments it is

found that the mesial surface of the hemisphere near the crucial sulcus (prorean and presplenial convolutions) gives the most marked effect, but I have also found that the anterior part of the third or median convolution (coronal or anterior supra-Sylvian) gives a very constant effect. In one or two instances there was a transitory constriction of the pupils before the dilatation from this area. Ferrier obtained constriction of the pupils and divergence of the eyeballs from this spot in the dog, but I have not observed the latter effect in the cat.

In the occipital region, what may be called the focal spot is in the posterior part of the third or median convolution (posterior supra-Sylvian convolution). I have not observed any constriction of the pupil here, as described by Ferrier. François-Franck, however, obtained a transitory constriction from this spot, followed by dilatation, exactly like that which I describe for the coronal gyrus. It is, therefore probable that there are foci for pupil constriction both in the frontal and occipital areas, but that they are masked by the dilator effects, which are much more readily produced. One may compare with this the greater representation of lateral eye movements over any other eye movements in the cortex.

Only the results which are deduced from a large number of carefully planned experiments can be considered trustworthy, more particularly in deciding between areas which give a positive result independently of epileptoid convulsions. These are very readily brought about by repeated excitation of the same or closely neighbouring areas, owing to the increased excitability of the cortex which is thereby induced. The condition of anæsthesia is also of the utmost importance. If this is deep, the pupils remain immobile. If it is too light, dilatation is obtained from almost every part of the cortex, at any rate when bodily movements occur. The results are only reliable when the anæsthesia is moderate.

(B) *Dog*.—The areas are very much the same in the dog as

in the cat. This animal is less suited for the purpose because of the rarity of dogs with light-coloured irides, and a round pupil is less easy to detect slight variations upon than the slit-like one of the cat. In the dog I obtained a very marked effect from the precrucial gyrus, but I failed to observe any convergence of the optic axes as noted by Ferrier.

(c) *Monkey*.—I have done only one experiment of this nature upon the monkey. I found it much the easiest animal to work with, and it gave very definite results.

We conclude, therefore, that previous section of the cervical sympathetic diminishes the effect, but by no means abolishes it. When both cervical sympathetics are intact, the dilatation of the pupil, when well marked, is accompanied by all the usual effects of excitation of the nerves themselves, viz., retraction of the nictitating membrane, widening of the palpebral aperture and projection of the eyeball; to these, Bechterew and Mislowski add secretion of the lacrymal gland, but this I am unable definitely to confirm. All these effects are abolished by previous section of the sympathetics except the dilatation of the pupils, and this is diminished. Whereas when the nerves are intact full dilatation of the pupils may occur, especially during epileptoid convulsions; after they are divided, the pupils rarely become more than three-fourths dilated. The effect is very well seen if one nerve is divided, the other being intact. In this case the two pupils move synchronously and apparently to the same extent, except that they start unequal, the one on the divided side being the smaller. François-Franck is, therefore, certainly wrong in asserting that the pupillary dilatation is unilateral if one sympathetic has been cut. He certainly admits a slight degree of dilatation, which he attributes to dilator fibres running another course, probably in the trigeminal. I have eliminated this possibility by dividing the fifth nerve intracranially, and still obtaining the undiminished effect. To eliminate the possibility of other dilator fibres reaching the superior cervical ganglion I have, as already stated, extirpated it. The pupil on the side from which the ganglion was

removed was slightly but appreciably smaller than on the side on which the vago-sympathetic was cut.

I have found that section of the third nerve intracranially after previous division of the cervical sympathetic causes the pupil to become immobile, about three-fourths dilated. Stimulation of the cortex has then no effect upon it.

Complete section of the corpus callosum has no effect upon the result of exciting the cortex. The bilateral effect is, therefore, not due to the stimulus acting through the opposite cortical areas, but to its acting upon lower centres, but whether the optic thalami or the superior colliculi, or the sub-collicular nuclei I am not prepared to say, but probably upon the last mentioned.

Stimulation of the anterior and posterior parts of the corona radiata and internal capsule containing the fibres derived from the cells of the frontal and occipital areas leads to bilateral dilatation of the pupils. I have generally found a stronger excitation necessary, but this may be due to the fact that stimulation took place at the end of prolonged experiments. In one case I obtained a very marked constriction of the pupils, with strong convergence of the eyeballs from stimulation of the posterior part of the internal capsule.

A point of great interest arising from these experiments is the question of the mechanism whereby dilatation of the pupils can occur in the absence of the usual dilator tract. Two explanations offer themselves, viz., inhibition of the tonic action of the third nuclei, and dilatation brought about by vascular changes in the iris. An extremely interesting observation by Sherrington may be mentioned in this connection. In bringing physiological experiment to bear upon current theories of the emotions, he performed "appropriate spinal and vagal transection" in the dog to eliminate "the sensation of all the viscera and muscles below the shoulder." He says:—"The eyes were well opened, and the pupil distinctly dilated in the paroxysm of anger. Since the brain had been, by transection, shut out from discharging impulses

via the cervical sympathetic, the dilatation of the pupil must have occurred by inhibition of the action of the oculo-motor centre."

It is said that after the optic nerves have been cut, dilatation of the pupil is not obtained upon section of the third nerve, and hence tonic action of the third nuclei has sometimes been denied. There can be no question, however, that it exists when the optic nerves are intact, as in my experiments.

The immobility which follows section of both the third and the sympathetic is strong evidence in favour of the inhibition theory. It must be noted, however, that the blood pressure was probably very low at this stage of the experiment.

We have seen that dilatation of the pupil is still obtained after section of the sympathetic. No vaso-motor fibres are known to run to the iris, except by way of the sympathetic, and even if such exist, the experiments of Langley and Anderson tend to show that vascular effects are inefficient to bring about the dilatation observed. Moreover, it is well known that changes in blood pressure may occur from stimulation of various parts of the cortex, whereas pupil dilatation only occurs from certain localised spots in the absence of the epileptoid state.

It seems justifiable from these considerations to regard the effect as another example of direct inhibition of the oculo-motor nerves from the cortex.

There is no lack of evidence as to the presence of fibres connecting the cortex with the mesencephalon, and some of these must be regarded as the ones concerned in the pupillary effects. We may leave out of the question the dilatation of the pupil which accompanies the epileptoid state, for this is undoubtedly of an extremely complex nature, requiring special investigation. Confining our attention to the more specialised results obtained from the oculo-motor area in the posterior part of the frontal convolutions, which are to be looked upon as part of the fronto-parietal motor or kinæsthetic

area and quite distinct from the more anterior or so-called pre-frontal area, and to the results obtained from the oculo-sensory or visual area in the occipital convolutions, we find definite anatomical connections with the lower centres.

The pallio-tectal or cortico-mesencephalic system of fibres has recently been thoroughly investigated by Dr. Beevor and Sir Victor Horsley. It is noteworthy that no fibres were found passing to the mesencephalon from the frontal region, *i.e.*, from the area of cortex in front of the excitable cortex. From lesions of this part there was marked degeneration of the fronto-thalamic fibres previously described by Déjerine; the only mesencephalic centre to which fibres could be traced was the upper or anterior part of the locus niger. No fibres, therefore, go to the tectum.

A large number of fibres could be traced from the excitable cortex to the corpora quadrigemina and mesencephalon, especially to the superior colliculus. This was very marked in the cat, much less so in the monkey. The fibres from the oculo-motor areas have not yet been specially investigated.

The results from lesions of the occipital lobes were particularly striking, and confirmed Edinger's researches on birds. In proportion as more of the area of the cortex containing Gennari's streak is involved in the lesion the number of degenerated fibres passing to the colliculus increases. The fibres are large, and stand out distinctly from the medium-sized occipito-thalamic and occipito-geniculate fibres, and from the small callosal fibres and fine collaterals which enter the corona radiata in large numbers. Some of the occipito-tectal fibres pass among the fibres of Gratiolet's radiation, others run through the mesial region of the inferior longitudinal bundle. All the fibres are distributed to the whole breadth of the stratum griseum profundum of the superior colliculus.

Which of these fibres are concerned in the pupillary phenomena, and whether they pass, any of them, directly to the superior pupillo-dilator centre or to the pupillo-

constrictor centre, or only by intermediate connections, must be left for future research to determine. We have already shown that the cortical pupillo-dilatation is a complex event, strikingly resembling the ordinary sensory dilator reflex in that it is accompanied by all the usual effects of stimulation of the cervical sympathetic as long as that path is intact, but that it also occurs, deprived of the other sympathetic effects, when this nerve is divided. The evidence is, therefore, in favour of a more circuitous course, or at any rate of multiple and complicated interconnections. X

There is evidence that pupillo-constriction can also be elicited from stimulation of the cortex. Ferrier obtained it from stimulation of the anterior and posterior limbs of the angular gyrus in the monkey, but this observation is probably incorrect. I have already stated that, apart from a transitory constriction (*cf.* François-Franck and Pitres), I failed to confirm the same observer's results from the third external or coronal convolution in dogs. In pigeons, Ferrier found intense constriction of the pupil from excitation of the middle of the convexity of the hemisphere. Schäfer obtained marked constriction of the pupil from stimulation of the quadrate lobule in monkeys.

This brings us to the consideration of the exact nature of the phenomena. The view of Bechterew and Mislawski that we have here the central prolongations of the cervical sympathetic, is, *a priori*, highly improbable, or at any rate a misleading explanation of the results. Indeed, the continuance of the dilatation after section of the cervical sympathetic proves that it can only be partially true.

So, too, it is unlikely that we are dealing with "centres" for the pupils, in the ordinary sense of the term. We have found that the effect is most specifically obtained from the areas which are most concerned with ocular movements, whether from the motor or the sensory side. Moreover, it would seem that the effect is indissolubly connected with those movements, and does not occur in their absence. Hence it is most reasonable to conclude that the phe-

nomenon is an associated effect. As regards the so-called sensory areas, *i.e.*, the visual centres in the occipital cortex, it is probable that the attention plays some part. We produce, by artificial excitation, some strong, but probably ill-defined, visual sensation, which arouses the attention, and leads to the appropriate movement of the head and eyes towards the direction from which the stimulus seems to proceed. The sensation is strong and sudden, and is accompanied by dilatation of the pupils in no physiological sense other than the expression of emotion.

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THROMBOSIS OF THE CENTRAL VEIN OF THE RETINA.

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THE ophthalmoscopic condition known as "thrombosis of the central vein" is a sufficiently well recognised one. There are indeed certain borderland cases in which, although there are copious retinal hæmorrhages, one hesitates to make a definite statement because the signs of venous obstruction which are of primary importance in the diagnosis, are insufficiently marked. Yet there is usually but little difficulty in separating this from other hæmorrhagic conditions of the retina, and it may justifiably be given a place as a clinical entity. The object of the present paper, however, is to discuss the subject not from the clinical, but from the pathological point of view, on the basis of four cases which I have recently had the opportunity of examining microscopically,—to discuss in fact the question, "what is the pathological basis of the accepted clinical picture"?

Arguing merely from the clinical standpoint, when one sees the large hæmorrhages and the enormously swollen and tortuous veins, at one place buried in exudation, at another thrusting forth a knuckle, one is driven to the assumption that there must be something obstructing the venous return; and when one further finds that these appearances are usually confined to one eye, the other fundus being either normal or showing only slight vascular disease, while there is no proptosis or other evidence of obstruction of the ophthalmic vein, the conclusion seems inevitable that the obstruction must be in the central vein of that eye and not anywhere farther back. Arguing further *a priori* we find that these cases occur usually in elderly people, that in the form of thickened peripheral vessels and cardiac hypertrophy, there are often

signs of wide-spread vascular disease, and that in a certain proportion of instances there is evidence of nephritis. All these are conditions which tend to favour vascular obstruction, and which cases are indeed known to cause obstruction in the cerebral vessels ; hence it seems probable that in the case with which we are dealing, the obstruction in the central vein will be a thickening of the vein wall, or a thrombus within its lumen, or a combination of these two conditions. When now we find that loss of vision is usually sudden, or at least not very gradual, and that there are usually not any definite prodromal symptoms, it might be concluded that the occurrence of a thrombosis and not of a very gradually built-up thickening of the vein wall would most probably be the immediate cause of the loss of vision. Sclerosis of the vein wall would of course predispose to such a process of thrombosis.

We see, therefore, that the thrombus in the central vein which is commonly assumed to be present in these cases would theoretically account well for the clinical signs and symptoms, but when we turn to those recorded cases in which a pathological examination has been carried out, in order to find how far such theorising can be substantiated, we see that while a thrombus has indeed been discovered in a certain number of the cases, it has not been found in all. It is not necessary to introduce a discussion of all the literature into my text. This has been done frequently by different authors, and recently and sufficiently fully by Ischreyt. It will be useful, however, for ease of reference on special points, and because it seems not to have been done before, to briefly tabulate those cases from the literature in which a sufficiently full pathological examination has been made of the cases under consideration. I have omitted from the list two cases which Angelucci* reported as "thrombosis of the central vein," because it is practically certain that they were not of this nature. They occurred in young persons, there were no retinal hæmorrhages and but

* Angelucci, *Klin. Monatsbl. f. Aug.*, 1878, p. 443, ditto 1879, p. 151, ditto 1880, p. 21.

moderately dilated veins, the clinical history resembled that of embolism of the central artery, and indeed they both had aortic valvular disease. Michel,* who had the opportunity of examining Angelucci's specimens has recently stated his conviction that the appearances in his first case were due to a psammoma-like concretion lying outside the vein, and perhaps compressing the artery, while in his second case they were due to *post-mortem* coagula. Indeed, Angelucci reports a third case (which was not examined pathologically) in which there was retinal œdema, and the cherry-red spot at the macula, and includes these two as signs of thrombosis of the central vein! I have also excluded some cases in which a thrombus was mentioned, but in which insufficient details are given. A case of Juler's† for instance, a man of 39 who suffered from heart-disease, and had hæmorrhagic retinitis and glaucoma, in whose eye a "clot of a central vessel" was found. Also a case of hæmorrhagic glaucoma mentioned by Schnabel‡ in which he found "cellular infiltration round the vein and thrombosis of it."

It is also to be remarked that some of the cases included in the list are not altogether convincing. Michel seems to be not quite sure whether his own first case may not have been an obliteration of the vein by proliferation of the intima rather than a true thrombosis; the picture given of his second case rather suggests a leukæmic blood-clot with abundant leucocytes, while the picture of his third case also resembles a coagulum deposited from stagnant blood rather than a true *intra vitam* thrombus, *i.e.*, it shows neither the lamination of a recent thrombus nor the organisation of an old one. Similar appearances are not uncommon in the ciliary vessels and are noted in Case III below. The same remarks apply to Gauthier's case, and to Fridenberg's, and probably also to Würdemann's in which a "clot" is spoken of in both the artery and vein. In Meyerhof's case it is also doubtful

* Michel, Zeitsch. f. Augenh., pt. 2, 1899, p. 28.

† Juler, Brit. Med. Journ., 1896, September, p. 811.

‡ Schnabel, Arch. f. Augenh., vol. xxiv, p. 283, 1892.

Author.	Sex and age.	Albuminuria.	Evidence of vascular disease.	Clinical history.	Pathological examination.
1. Michel, 1878, Arch. f. Ophth., vol. xxiv, pt. 2, p. 37.	M., 53	None	General arterio-sclerosis, threatening of hemiplegia. P.M. Cardiac hypertrophy and mitral insufficiency.	Usual picture of "thrombosis of central vein" observed for 16 months without any great change. Eye obtained <i>post-mortem</i> .	Cellular thrombus $1\frac{1}{2}$ mm. long, 6 mm. from eyeball. Distended perivascular lymph-sheath and round-celled infiltration. Artery, thickened adventitia. Organised blood in vitreous.
2. Michel, 1878, Deutsch. Arch. f. Klin. Med., p. 306.	?	?	?	Retinal hæmorrhages found <i>post-mortem</i> in a case of leukæmia.	Thrombus (molecular detritus, round cells and red blood corp.), $1\frac{1}{2}$ mm. long at point of exit of vein from optic nerve.
3. Michel, 1899, Zeitsch. f. Aug., vol. ii, p. 1.	F., 37	Present	General arterio-sclerosis, hypertrophy of left ventricle.	"Retinitis albuminurica" both.	Thrombus in left central vein; homogeneous periphery, granular centre. Thought to be of 3-8 days' duration. Coagula in retinal veins. Retinal arteries thickened.
4. Deutschmann, 1879, Arch. f. Ophth., vol. xxxv, pt. 3, p. 163.	M., 72	?	?	Hgic. retinitis R.; veins tortuous. Glaucoma 9 months later. V. L. 6/12. O.E. normal.	No thrombus; hges. into optic nerves; central vessels normal. Corneo-iritic angle closed.
	M., 54	?	?	Hgic. retinitis R.; glaucoma 9 months later.	No thrombus; hyaline thickening of retinal vessel walls giving the amyloid reaction. Corneo-iritic < closed.

Author.	Sex and age.	Albuminuria.	Evidence of vascular disease.	Clinical history.	Pathological examination.
5. Wagenmann, 1892, Arch. f. Ophth., vol. xxxviii, pt. 3, p. 213.	M., 66	None	Arteriosclerosis cardiac hypertrophy.	Hgic. retinitis R. coming on in the night; glaucoma 1 month, and excision 3 months later. L. normal.	No thrombus; endarteritis in central artery and ? multiple emboli in retinal arteries. Very little change in veins. A.C. < closed.
	M., 76	Trace	Arteriosclerosis; three attacks of agraphia.	Hgic. retinitis; 7 months later glaucoma and corneal ulcer; 1 year after onset, enucleation. V. L. 6/6.	Thrombus; finely granular mass without nuclei projecting half-way into lumen of vein, remaining space being filled with blood. Veins and arteries both thick-walled and with proliferation of intima. A.C. < closed.
	M., 42	None	None	Hgic. retinitis R. L. normal. 4 months later iritis with post. synechia and glaucoma. Excision 5 months from onset.	No thrombus. Retinal vessels much thickened; endothelial proliferation; sometimes quite closed. Hyaline degeneration. Inflammatory foci A.C. < blocked.
6. Weinbaum, 1892, Arch. f. Ophth., vol. xxxviii, pt. 3, p. 191.	M., 26	None	None	Sudden D.V. of R.; 2 months later, when first seen, glaucoma and hgic. retinitis. Iridectomy followed by hgic. Excision 14 months after onset. V. L. = 6/6. O.E. normal.	Thrombus $\frac{3}{4}$ mm. long, $1\frac{1}{2}$ mm. behind lamina cribrosa. Scaffolding of fibres and spindle-cells with some nests of round-cells between. Cleft between it and wall filled with blood. Vein elsewhere of normal lumen. A.C. < closed.

7. Purtscher, 1896, Arch. f. Augenh. Ergänzungsheft, p. 1.	F., 21	None	..	Liabile to epi- staxis.	D.V. R. 2 months. Glaucoma when first seen. Excision 3 months after onset. Hgic. retinitis found on bisecting eye. L. retinitis proliferans and hgcs.	Thrombus 0.6 mm. long central to lamina; organising, leaving a little space at one side. Retinal vessels hyaline; new-formed tissue in vitreous. A.C. < closed.
8. Stölking, 1897, Arch. f. Ophth., vol. xliii, pt. 2, p. 306.	F., 65	None	..	Cardiac irregu- larity. No ri- gidity of peri- pheral vessels.	Hgic. retinitis R.; 1 month later glaucoma. Iridectomy. Excision 3 months from onset. V. L. 4/6.	No thrombus. Narrowing of both artery and vein at lamina. Hyaline degene- ration of retinal vessels. A.C. < not closed.
9. Goh, 1897, Arch. f. Ophth., vol. xliii, pt. 1, p. 147.	M., 25	Tube-casts	..	None	Hgic. retinitis on both sides 3 days before death from stomatitis gangrenosa and septicæmia. Veins enlarged and tortuous. Many new hgcs. before death.	R. Recent marantic thrombus 1 mm. behind lamina, leaving a small lumen at one side. Retinal vessels normal, but distended. L. No thrombus in central vessels; thrombi in smallest retinal vessels.
10. Alt, 1897, Amer. Journ. Ophth., p. 114.	F., 64	Doubtful trace	..	None	D.V. R. 3 weeks. Large ma- cular and many small hgcs. Vessels dark and tortuous. 4 weeks later glaucoma; more retinal hgcs. hyphæma. Excision 2 weeks later. L. V. = 20/100. 3 D. Hm.	"Thrombosis and thrombophlebitis" of larger retinal veins and "pigmentary degeneration" of smaller. Central vessels not described. A.C. < shut off.

Author.	Sex and age.	Albuminuria.	Evidence of vascular disease.	Clinical history.	Pathological examination.
11. Fridenberg, 1897, Arch. f. Aug., vol. xxxiv, p. 175.	M., 70	Albumen and tube-casts	?	Hgic. retinitis and glaucoma. D.V. had lasted 1 year, but 1½ years before its onset a small retinal hge. had been accidentally found on testing for glasses. Iridectomy, but 3 weeks later hyphæma and high tension. Excision.	"Hyaline thrombi" in many vessels, especially on the disc. Walls of central and retinal veins normal. Hyaline degeneration and proliferation of intima in arteries. A.C. < blocked.
12. Bankwitz, 1898, Arch. f. Ophth., vol. xiv, pt. 2, p. 384.	F., 72	?	Arteriosclerosis. Several apoplectic strokes. Right hemiplegia.	Hgic. retinitis. D.V. R. (first noticed on awaking) of 5 weeks' duration. Later glaucoma, iritis, posterior synochæ. Excision 2 months after onset. L. cataract incip. O.E. normal. V. = 6/18.	Small aneurism on artery in front of lamina supposed to have obstructed vein and caused thrombosis of it. Retinal arteries much thickened, in places obliterated. Veins also thick, some containing thrombi, others crammed with blood.
13. Türk, 1898, Deutschm. Beitr. z. Augenh., Heft. xxiv, p. 45.	M., 67	None	Cardiac irregularity. Endocarditis P.M.	Hgic. retinitis L. D.V. 4 weeks previously. Patient died 9 days later. No glaucoma. R. with -0.5 D. sph. = 6/12. Incipient cataract.	Organising thrombus, 1 mm. long, just behind lamina. Fully fills vein in front, leaves clefts behind. Vessel walls normal in nerve, slight thickenings in retina. A.C. < blocked.

14. Würendemann, 1898, Deutschm. Beitr. z. Aug., Heft. xxix, p. 100.	M., 8	None	..	..	Hgic. retinitis L. coming on 14 days after mumps (patient seemed quite recovered). 1 year later acute glaucoma; excision. V. R. 6/6 normal.	"Clot" in artery from 1 mm. behind lamina backwards for 5 mm.; small clot in vein not completely occluding lumen. New-formed tissue in vitreous. A.C. < closed.
15. Reimar, 1899, Arch. f. Aug., vol. xxxviii, p. 209.	F., 57	None	..	General arterio- sclerosis.	Hgic. retinitis with greatly tor- tuous veins of 5-6 weeks' du- ration. 8 months later glau- coma; slight iritis. Scler- otomy unsuccessful. Exci- sion.	No thrombus. Veins partly normal, partly much thickened. Endarteritis in central and retinal arteries, and some small miliary aneurisms in latter. Vitreous hæmorrhage. A.C. < closed.
16. Gauthier, 1898, Annales d'oculi- stique, vol. exix, p. 438.	M., 45	None	..	?	First seen with iritis R. Glau- coma followed, for which sclerotomy and iridectomy done, and fundus now first visible showed hges. Glau- coma reappeared. Excision.	Central vein contained hyaline mass extending from lamina into main branches. Lumen completely ob- structed in some places, partly in others. Iris adherent to lens. A.C. < not mentioned.
17. Meyerhof, 1900, Zeitsch. f. Augenh., pt. 4, p. 676.	M., 50	None	..	Slight arterio- sclerosis; sys- tolic murmur.	L. Hgic. retinitis. R.V. 6/6. 9 years later glaucoma L.; iridectomy; relief. Again glaucoma, 1 year later. Ex- cision. V. R. still 6/6, but later some hges.	Central vessels normal; in retina thick- ening of media and adventitia. Dark red masses in lumina? thrombi of both arteries and veins.

Author.	Sex and age.	Albuminuria.	Evidence of vascular disease.	Clinical history.	Pathological examination.
18. Ischreyt, 1900, <i>Arch. f. Augenh.</i> , vol. xli, p. 38.	M., ?	None	General arterio- sclerosis.	1st symptom = scotoma before R.; not examined at time. 2 months later glaucoma and fundus invisible. Excision. Copious hges. in every part of retina. V. L. with -4 sph. = 6/12. O.E. normal.	Thrombi in super. and infer. nasal veins and walls thick and hyaline. Central vein normal. Endarteritis of central and retinal arteries, and hyaline thickening of retinal. A.C. < closed.
19. Yamaguchi, 1903, <i>Klin. f. Aug.</i> <i>Beilageheft</i> , p. 180.	M., 25	?	None	Signs of cerebral tumour. Optic neuritis going on to atrophy. 1 year later recurrence of choked disc with many reti- nal hges. Typical picture of thrombosis of central vein. Obtained <i>P.M.</i>	While crossing the vaginal space vein narrowed by contraction of cicatricial tissue. Thrombotic masses lying against wall. No endothelial pro- liferation, but wall hyaline.

whether we are dealing with true thrombi or with coagula. Bankwitz's explanation of an aneurism on the artery obstructing the vein sounds improbable, while Goh's case belongs to a somewhat different category from those under consideration, since it occurred during an exhausting illness and only a few days before death.

Shortly to summarise the different pathological changes which have been put forward in explanation of the clinical picture of "thrombosis of the central vein" we have: (1) A thrombus in the central vein in 11 out of 22 cases; (2) Occlusion of the central vein by proliferation of the intima, but without thrombosis (possibly in Michel's first case); (3) Multiple thrombi in the retinal veins, but without a thrombus in the central vein (Alt, Ischreyt); (4) Multiple emboli, or perhaps thrombi in the retinal arteries (Wagenmann, Case I).^{*} Stölting seems to regard his case as of the same sort. In Fridenberg's and Meyerhof's cases there were thrombi (or coagula) in both the arteries and veins; (5) Changes in the retinal vessels (hyaline thickening, endarteritis, endophlebitis) sometimes amounting to occlusion, but not the result of either thrombosis or embolism (Wagenmann, Case III, Deutschmann, Case II, Reimar); (6) Hæmorrhage into the substance of the optic nerve (Deutschmann, Case I).

No remarks are needed on the first three of these explanations, since it is sufficiently obvious how the ophthalmoscopic appearances might be produced by them. With regard to No. 5 also there is no insuperable difficulty in accounting for the clinical picture if we suppose the thickening to fall chiefly on the vein walls and to produce obstruction of the venous current. It is not so plain, however, why lesions on the arterial side of the circulation, whether emboli, thrombi, or endarteritis, should give rise to the appearances of venous obstruction and to the copious hæmorrhages. The explanation usually given is that we are really dealing with multiple

^{*} Wagenmann at first regarded the lesions as multiple emboli of the arteries, but has recently (Sitzungsbericht der Ophth. Gesellsch. z. Heidelberg, 1898, p. 251) given his opinion that they may have been thrombi.

hæmorrhagic infarcts such as occur when the pulmonary or any end artery is blocked, *i.e.*, that when an obstruction occurs in an artery to which there are no sufficient collaterals, and when in consequence the blood-flow through the corresponding vein is stopped, there occurs a back flow of venous blood in a direction the reverse of the usual, which causes engorgement of the vein and hæmorrhages from it. A case of Knapp's* is usually quoted in which the ophthalmoscopic appearances seemed to indicate that there had occurred an embolism of a single arterial branch in the retina, and in which the corresponding vein was engorged and accompanied by hæmorrhages. Haab,† however, has suggested that the real explanation of this case was that a thrombus in the vein had been the primary lesion, and that in consequence of the obstruction to the blood-flow an endarteritis had been set up in the artery, which gave it the thin appearance of an artery in which an embolus had lodged. It has been abundantly proved, and is indeed a matter of common experience, that branch embolism, like embolism of the main trunk, is not usually followed by any such hæmorrhages as those described in Knapp's case. Haab‡ quotes 20 authorities in support of this statement, and in three cases of branch embolism personally observed I never saw any trace of hæmorrhage. It must therefore be considered doubtful whether obstructions on the arterial side of the circulation do offer any explanation of the ophthalmoscopic appearances in these cases. Deutschmann's finding of hæmorrhages in the optic nerve as a cause of "thrombosis of the central vein" has, so far as I know, never been repeated. The frequency of the occurrence of glaucoma in the cases tabulated may be merely noticed at present. I shall return to this point later.

Certain questions arise on studying these results. Is the clinical picture known as "thrombosis of the central vein" capable of being produced by more than one kind of

* Knapp, Arch. f. Augenh., vol. i, p. 29, 1869.

† Haab, System of Dis. of the Eye, Norris and Oliver, vol. iv, p. 519.

‡ Haab, *ibid.*, p. 505.

lesion, as is suggested by the variety of the findings in the above list? If so, have we any means of distinguishing clinically what lesion is present in any given case? If not, if there is some constant pathological entity as the basis of the well-defined clinical entity, how can we reconcile the variety in the pathological explanations which have been brought forward in different cases? It must be said that these questions cannot yet be answered with any degree of certainty, and though it is now 26 years since Michel published the first case, there is still need for the collection of fresh material, for it is only by having at our disposal a large number of reports, so far as possible clinical as well as pathological, that we can hope to come to a final conclusion. We find in the literature more than one case in which all the appearances clinically pointed to venous obstruction, and yet on pathological examination no thrombus or other impediment was found in the veins. It is possible that in some of these cases there really was an obstruction to the vein, which was overlooked in the pathological examination. Such a possibility exists, of course, where the whole length of the vein has not been examined in serial section, and in order that no part may be overlooked it is always desirable that the optic nerve entrance should also be cut in *transverse* serial section, and not horizontally in the usual manner. It is notoriously difficult to speak with certainty as to whether the lumen of a vessel is free or occluded, and as to whether its walls are thickened or not, when the vessel is cut longitudinally, for if the section does not happen to travel exactly up the centre of the lumen without any obliquity it is almost impossible to be sure of the condition of the vessel wall, and more especially is this the case when the vessel is collapsed and folded. A study of the literature and of the cases recorded below will show that the favourite seat for the lodgment of thrombi is either at the lamina cribrosa or a short distance behind it, probably because (Hertel), the central vessels narrow as they go through. The place where the central vein makes its exit from the nerve is also stated

by Michel to be a favourite seat, from the obliquity of the course of the vessel in this position, but a case of his own (No. 2 above) and one of Yamaguchi's (No. 19) seem to be the only ones on record of thrombus in this position. It may, therefore, easily happen that a thrombus may be overlooked, on the one hand at the lamina because the sections have been longitudinal to the nerve, and on the other hand at the exit of the vein from the nerve if this point be not included in the piece of nerve excised.

There is a further difficulty in the interpretation of the pathological appearances in some of these cases. In many of them the initial lesion occurred long before the eye came to excision, and during part of that time glaucoma was present. It becomes difficult to say, therefore, what changes were primary and what secondary, for it is likely that in an eye long the subject of glaucoma, interference with the intraocular circulation will itself give rise to vascular changes and even to thrombosis in the retinal veins, and though it is improbable that increased intraocular tension should give rise to a thrombosis in the central vein behind the lamina, yet even this is possible as a result of slowing of the intraocular circulation. Then, again, it does not follow in every case of glaucoma in which on bisecting the eye retinal hæmorrhages are found, that these hæmorrhages have preceded the onset of glaucoma, as is the usual history in true cases of thrombosis of the central vein. For in any glaucomatous eye in which the vessels are extensively diseased, hæmorrhages will be liable to occur, and more especially will this be the case if the tension have been suddenly relieved by opening the anterior chamber for the performance of an iridectomy or sclerotomy. Analogous cases are furnished by the hæmorrhages which sometimes ensue on too quickly and completely withdrawing fluid from the pleural cavity, or from a much over-distended bladder. It is necessary, therefore, in each case, unless it is known from actual observation that the retinal hæmorrhages preceded the glaucoma, to weigh the clinical with the pathological evidence before coming to a conclusion with regard to the sequence of events. If a history be given of

sudden loss of vision in the form of clouds and mist before the eyes, perhaps noticed on waking in the morning, if there have been at first no pain or redness of the eyeball, but if these symptoms have made their appearance later, then the probability is strong that the case was indeed first one of thrombosis of the central vein upon which glaucoma ensued. If, on the other hand, the history be of loss of vision with supraorbital neuralgia, pericorneal redness and rainbows round lights, then it is probable that the glaucoma was the first fact and that the hæmorrhages ensued later, either as a consequence of vascular disease or as a result of operative interference.

The following, then, are desirable conditions in the material upon which we conduct our investigations on thrombosis of the central vein. The disease should not have lasted too long, otherwise it will be difficult to separate primary from secondary lesions. Glaucoma should not have been present, since it complicates matters, or if it has been present (for we seldom obtain pathological material in which it has not occurred), it should not have lasted long enough to mask the earlier condition of affairs. It should be known by actual observation, or rendered probable by the history of the case, that the hæmorrhagic retinitis and not the glaucoma was the first factor in the case. The eye should not have been too much interfered with by operation. The eye should be cut in serial section, and more especially the disc and lamina cribrosa should be cut in transverse serial section. All these conditions are seldom fulfilled in one case, but some of them were present in Case 1 to which we may now pass.

CASE I.

Mrs. S., æt. 45, a cook, was admitted to the R.L.O.H. on 15.vi.03, under Mr. Treacher Collins. She was a very stout woman, and somewhat breathless on exertion, but, except for gall-stones 15 years before, she had never had any serious illness, and she believed herself to be in perfect health. She was accustomed to work in a rather hot place, and had to do a

good deal of stooping, but her work did not subject her to any great physical exertions.

Four days before her admission—on the afternoon of June 11th—while she was sitting quietly and reading a book, there came a sudden mistiness over the sight of the right eye, on account of which she kept rubbing her spectacles. This increased in density until, by next morning, she was practically blind in that eye. Since then there had been some movements in the clouds before the eye, but vision had remained in the same state.

The pulse numbered 62, and was regular; the radial and superficial temporal arteries were not appreciably rigid. No abnormality was detected in the heart or lungs, though auscultation was difficult on account of her stoutness. The urine was acid. Sp. gr. 1007. Abundant albumen. No sugar.

The right pupil reacted consensually, but not directly, the left normally. The external appearance of the eyes was otherwise normal.

V.R. = shadows. V.L. 6/12, with - 0.5 cyl. Ax. H. = 6/6 letters. O.E.R. The disc was congested and hazy; no definite margin was visible, and, in the surrounding retina, there were large masses of exudation spreading out on all sides, but roughly following the lines of the main vessels. The arteries were often invisible, but, where seen, were apparently of about the normal calibre. The veins were greatly enlarged, and very tortuous and dark, especially one proceeding upwards. They were often entirely buried in exudation, while here and there a tortuous knuckle looked through. On the disc they were for the most part invisible. Scattered everywhere throughout the fundus there were innumerable hæmorrhages, small and large, striate, rounded, and irregular. The disc was but little, if at all, swollen above the level of the surrounding retina.

O.E.L. The relations of the veins to the arteries was normal, and there were no vascular changes or hæmorrhages. The disc was normal. There were a few sharply-defined, glistening yellow specks to the nasal side of the disc, which were believed to be outgrowths of the lamina vitrea.

She was seen again on June 22nd, when the ophthalmoscopic appearances were unaltered.

24.vi.03. She was admitted with glaucoma. T + 1. Cornea

a little steamy. Pericorneal congestion. Anterior chamber *deep*. Pupil semi-dilated and fixed. The media were too opaque to allow of any examination of the fundus, but, knowing of the presence of retinal hæmorrhages and of the exceedingly bad prognosis for operative interference in these cases, Mr. Collins decided merely to paracentese the anterior chamber, and not to attempt an iridectomy or sclerotomy in the first place. This was accordingly done, and the aqueous was let off as slowly as possible (the patient was very restive), yet a minute stream of hæmorrhage was seen to come from two places in the iris.

This operation relieved the tension at the time, but the patient became very ill, took suppression of urine, and died on July 1st. The eye was obtained *post-mortem*, but a full autopsy was not performed. The globe was hardened in 10-per-cent. formol, and bisected horizontally.

Macroscopic Examination.—The anterior chamber was of good depth. It contained no blood, and the angles did not look blocked. The retina was strewn with hæmorrhages, but there were none in the vitreous.

Microscopic Examination.—The optic nerve was shaved off close to the globe, and cut in serial section, every 5th section being mounted. The globe itself was cut in serial section, every 10th section being mounted until the edge of the disc was reached, when every 5th and in the centre all the sections were prepared. The piece of nerve remaining with the eyeball was unfortunately cut longitudinally.

Cornea.—Normal.

Corneo-iritic Angle.—On the temporal side, the iris is adherent to the extent of about one-half of the ligamentum pectinatum. It is a true adhesion, and not a mere apposition of iris and ligamentum, since new formed fibrous tissue can be seen crossing from the one to the other, and it is not torn in any of the sections. It nowhere reaches as far as the membrane of Descemet, and the ligamentum pectinatum preserves its usual spongy texture, and seems as if drainage could still go on well through it. There is a good deal of brown granular pigment among the trabeculæ, and this reaches forward a little distance between the membrane of Descemet and the deepest layers of the corneal stroma. In a few sections there are some blood

corpuscles in the spaces of Fontana. The canal of Schlemm is normal, and contains no blood. On the nasal side the blocking is very slight, and is probably more an apposition than a true occlusion. The angle is never rounded, but the connection of iris and ligamentum pectinatum by fibrous tissue is lacking. There is some homogeneous coagulum in the anterior chamber at the angle.

Iris.—The iris stroma is normal. There are no inflammatory foci in it, but near the root there are a few small hæmorrhages. Some of the vessels show very great thickening of their walls, even taking into account that the iris vessels are normally thick-walled for their size. Both the endothelium and outer coats are affected; we have most internally a layer, three or four cells deep, of well-stained ovoid nuclei surrounding a very narrow lumen; then comes a broad, almost homogeneous, layer, taking on the eosin staining but little, and showing only a very few elongated nuclei; outside of this, again, the pigment cells of the iris stroma are arranged so as to form an outer ring. These changes are best marked near the root of the iris on the adherent side, they are only slightly present on the non-adherent side, and in the smaller vessels near the pupillary margin. They sometimes cause total obliteration of the vessel concerned.

Ciliary Body and Choroid.—The ciliary muscle is normal. There are some hyaline-looking masses in some of the processes. The circulus major shows no endarteritis, but there are some small sclerosed vessels near the root of the iris. In the choroid there are hyaline outgrowths of the membrane of Bruch, which are mostly small, but some of which project through the pigment epithelium. The choroidal vessels are normal; some of them have a great many leucocytes within their lumina, and this is especially so on the temporal side.

Retina.—The retina shows the changes usual in hæmorrhagic "retinitis," no true inflammatory appearances, but merely distortion from the out-pouring of blood among its layers. The hæmorrhages are very abundant, but not usually of large size, so that the retinal layers are fairly well preserved. They are present for the most part in the inner layers, but sometimes extend through the outer nuclear layer, and are occasionally sub-retinal. There is no sign of their having broken through

the membrana limitans interna, and there is no blood in the vitreous. They are largest near the disc and become smaller in the periphery. Between the outer granular and outer nuclear layers there are some homogeneous coagula and fibrinous masses of small size. The retina near the ora serrata is vacuolated; the pars ciliaris normal.

Retinal and Central Vessels.—These showed the changes of most importance in the case. For convenience they will be taken together, and both arteries and veins will be traced backwards from the retina through the nerve. Much assistance was afforded in the study of the changes in these vessels by the use of Weigert's elastic tissue stain, which greatly helps in the case of the retinal vessels in distinguishing arteries from veins, since there seems to be no elastic tissue in the walls of the latter. In the case of the central vessels it picks out the elastica interna of the artery, and shows very beautifully the presence and extent of any endarteritis which may be present. The *retinal arteries* then show a very marked thickening of their walls, which causes great narrowing of their lumina, usually in an eccentric manner (fig. 1). As is shown by Weigert's stain, it is entirely within the elastica interna, and consists, therefore, of a proliferation of the intima. The cells composing it are large, with a clear, and sometimes with a vacuolated, cell-substance, and there is usually a well-preserved endothelial lining towards the lumen. These changes are most marked in the larger vessels near the disc, but are also present far out into the periphery. As it comes through the lamina cribrosa the artery has a good clear lumen and shows but little sign of endarteritis. Farther back there is again more endarteritis, which Weigert's stain resolves into a large number of curly fibres within the true elastica, some quite small and fine, others larger and coarser, and forming as it were little pieces of elastic membrane within the membrane of Henle proper, each reaching a little way round the lumen, but none completely round. Among these curly fibres the nuclei of the intima are to be seen.* This condition of the artery remains until it leaves the nerve. Outside of the nerve it is much collapsed and folded, and still shows endarteritis, but both here and within the nerve the endarteritis is moderate and

* See some excellent pictures of this condition in a paper by Hertel (Arch. f. Ophth., vol. lii, pt. 2, p. 191).

the lumen not greatly narrowed. The *retinal veins* show very great changes indeed, of which an example is given in fig. 2. Considering the extreme tenuity of the walls of the normal retinal veins, it is at first sight difficult to believe that this is really a vein, but it can easily be proved to be so by following the vessels in the serial sections from the disc. It also refuses to take on Weigert's stain, and with this reagent gives the same appearance as the vessel to the left in fig. 1. It will be noticed that there is a very small blood-filled lumen, and that the layers next this lumen have a more granular aspect than the outer layers, take on eosin staining more freely, and have more rounded nuclei. These layers I take to represent proliferated endothelium. Outside we have a layer whose groundwork is more homogeneous and whose nuclei are fewer and more elongated. This I take to be the thickened connective tissue wall of the vein (there is, of course, no true media in the retinal veins). The wide space around the vessel is probably not an artefact, but the greatly dilated perivascular lymph space, and no doubt corresponds to the masses of exudation seen with the ophthalmoscope. Coagulated exudation will also be noticed in the inner layers of the surrounding retina. The membrana limitans interna is seen to pass over the vein without being broken through. These changes also are more marked towards the posterior pole of the eye, but are also present in the peripheral vessels. The peripheral veins are much engorged in places, those near the disc only very moderately so. As the veins pass on to the disc and through the lamina their lumina continue very narrow and their walls extremely thick, but as they do not unite to form the central vein for some distance back in the nerve, and as they are cut longitudinally at the optic nerve entrance, it is impossible to make any very definite statement as to how much obstruction would be caused, and as to whether any of them are obliterated. The surrounding connective tissue is much condensed. Coming now to the course of the vein *in the nerve*, it is at first divided into three or four branches, of which one only is very considerably thickened. These join together a little way behind the lamina, and the whole wall is now thicker than normal. Weigert's stain shows that there is much elastic tissue in the wall, and since the vein is collapsed and folded a false resemblance is given to a crenated membrane

such as occurs in the artery. That it is not a true *elastica interna* is shown by the high power, which resolves it into a large number of fine and coarse wavy fibres (fig. 3). Inside of this there is a tolerably thick layer of proliferated intima with scanty pale nuclei, and towards the lumen there is a pretty regular layer of endothelium. The lumen must be to a certain extent encroached upon, but it is still fairly large. It contains no blood. These conditions remain unchanged until the vein leaves the nerve, when it is much collapsed and folded, presenting merely a slit in the connective tissue, but always with an endothelium-clothed lumen. At no point is the vein completely obliterated, nor is any laminated or organised thrombus to be found within it.

Optic Nerve.—The optic nerve itself shows no atrophy. The sheaths are normal and the intervaginal space not dilated. There are a few concentric concretions between the arachnoid and dura and in the dura. There is no glaucomatous cupping.

This is in many respects an interesting case. It was followed closely practically from beginning to end, and undoubtedly presented the typical picture of thrombosis of the central vein with numerous hæmorrhages, and, what is of much greater importance to the diagnosis, greatly swollen and tortuous veins. There followed with unusual swiftness glaucoma, the eye suffered no more operative interference than a paracentesis, and was obtained for pathological examination just 21 days after the first dimness of vision and 8 days after the onset of glaucoma, so that it may be believed that no very extensive secondary changes had taken place. Yet no thrombus was found in the central vein, although it was examined to beyond its point of exit from the nerve. Outside of the nerve it was much collapsed, and there was thickening of the intima, but the lumen was not occluded. Inside the nerve there was a similar condition of the intima, but the lumen seemed easily sufficient for the transmission of the blood. The optic nerve entrance was unfortunately cut longitudinally, so that we cannot be quite certain as to what size the lumen was, as the vessel came through the lamina, but it may be said with certainty

that the thickening of the vein increased greatly at this point, and that the lumen was correspondingly reduced. Yet here also it seemed not to be completely obliterated. The retinal veins showed a thickening which, when we remember their extreme tenuity under normal conditions, can only be described as enormous.

The case also illustrates certain points with regard to the relation of glaucoma to these cases of hæmorrhagic retinitis, but I shall return to this subject later in discussing the subject from a more general stand-point. It is noteworthy in this case that the corneo-iritic angle was only very slightly blocked, and that the portion of the ligamentum pectinatum, against which the root of the iris did not rest, was quite free and spongy in texture, and seemed as if it ought to provide tolerably free drainage. This slight blocking is merely a stage towards a more extensive adhesion of the iris, and greater condensation of the ligamentum pectinatum, which is always to be found where glaucoma has long endured in these cases. It is evident that, however the glaucoma arises in the first place (and I shall discuss this later), it tends, the longer it endures, to perpetuate itself the more firmly by oblitative tissue changes at the corneo-iritic angle. In the cases to be mentioned immediately a more advanced condition of the same process will be described.

An interesting minor point is the finding of glistening yellow specks with the ophthalmoscope in one eye and of outgrowths of the membrane of Bruch with the microscope in the other, which makes the probability strong that such outgrowths are really the cause of these yellow specks.

Looking at the case as a whole then, the proof that there was any thrombosis to account for the clinical picture fails; the obstruction to the vein, which was evident with the ophthalmoscope, seems to have been entirely due to narrowing of the lumen in consequence of thickening of the vein wall (endo and periphlebitis), probably the result of a general angiosclerosis due to nephritis. Since, however, the

vessels as they passed into the eye were cut longitudinally, and not transversely, the possibility of a shrunken thrombus having been overlooked in this situation is not to be entirely set aside, for such a thrombus would explain better than a gradual process of obliteration the sudden loss of vision which characterised the clinical history. There is some proof that the site of obstruction was on the disc itself, inasmuch as the ophthalmoscope showed the veins greatly enlarged in the periphery, but hardly visible on the disc, while the microscope showed that the thickening of the vein walls was greatest on the disc, and that the veins central to the lamina were not engorged as they should have been if an obstruction had existed further back, but rather small, empty, and collapsed.

The following case presented a somewhat less typical history, but the pathological examination gave some results of importance. It was under the care of Mr. Simeon Snell, who has kindly furnished the clinical notes:—

CASE II.

“Mr. D., æt. 53, consulted me on May 31st, 1902, and stated that in September, 1901, he was seized with giddiness, lost consciousness for 2 days, and on recovery was blind in both eyes. He recovered and was able to do things well until March, 1902. Then another attack came on, and since then he has been blind in the left eye. Vision in right is poor, 6/12. In the right there is haziness round disc (neuro-retinitis), but it is very little indeed compared to the left. In the left there is swelling of the disc with hæmorrhage. V. only l. p.

He has had 17 children, but only one is living, and that the youngest. He had syphilis 30 years ago. Not much headache or localising symptoms. Nose bleeds.

11.vi.02. A week ago he had seven fits. Right optic neuritis more intense. Left, a large number of fresh hæmorrhages like ecchymoses studded about the retina.

4.vii.02. Subsequently to last note he has had great pain with increased tension in left, and on this date the globe was removed.”

The eye was preserved in spirit ; it was shrunken and folded, but filled out again on immersion in 5 per cent. formalin.

Macroscopic Examination.—The corneo-iritic angle looks a little blocked. In the vitreous there is a coagulated exudate, but no fresh hæmorrhages. The retina is everywhere studded with hæmorrhages. The lens looks large, and nearly fills the interciliary space.

Microscopic Examination.—Serial sections were prepared of the globe as in the last case. The optic nerve was cut out along with the optic nerve entrance, and transverse serial sections were mounted from the retinal surface of the papilla through the lamina cribrosa and into the nerve.

Cornea Sclera, etc.—The cornea is normal. There is a moderate round-cell infiltration around the episcleral vessels and at the limbus, otherwise the sclera is normal.

Corneo-Iritic Angle.—As in the last case, the angle is much more extensively blocked on one side than on the other, the temporal. On the adherent side the occlusion is both more extensive—reaching nearly as far forward as the membrane of Descemet—and firmer. It is composed of fairly dense connective tissue, and the ligamentum pectinatum is itself much condensed, so that the spaces of Fontana are largely obliterated, and the canal of Schlemm, itself a mere slit, is shut off from any free communication with the anterior chamber. The ciliary processes are not pressed up against the root of the iris, but separated from it by a good interval. On the opposite side the amount of adhesion is nowhere so great, and, indeed, in some sections the angle looks almost free. The ligamentum pectinatum is also more spongy in texture, and the spaces of Fontana are patent, so that the canal of Schlemm, which is a wider channel than on the other side, seems to be open for drainage.

Iris, Ciliary Body, Choroid.—The iris stroma looks condensed and too cellular, but there are no definite inflammatory foci. The walls of the vessels are thickened, but there is no evidence of endothelial proliferation in this, as in the last case. A few small hæmorrhages are to be found in the substance of the iris near the corneo-iritic angle. There are no posterior synechiæ. The ciliary body is normal ; the muscle is rather small. The choroidal vessels are collapsed, but not otherwise abnormal.

Retina.—The retina shows innumerable large and small hæmorrhages with corresponding distortion of its elements. They are mostly in the nerve-fibre and ganglion-cell layers, and in places bulge the membrana limitans interna sharply towards the vitreous, without, however, penetrating it at any place visible in the sections. They also penetrate the nuclear layers, but nowhere become subretinal. The retinal layers are on the whole fairly well preserved, though there is a good deal of scattering of the nuclear layers here and there by the hæmorrhages. There are many fibrinous and homogeneous coagula in the nerve-fibre layer and between the two nuclear layers, with a corresponding separation of the structures in these situations.

Retinal and Central Vessels.—In the larger retinal arteries the changes are very moderate and consist in endarteritis. In the smaller the affection seems to be chiefly of the middle coat, which has a clear homogeneous appearance with but little nuclear staining, *i.e.*, hyaline degeneration. On the disc the arteries are very considerably thickened, and in some cases nearly obliterated. The thickening seems to affect the media chiefly, and is in the form of a somewhat homogenous ground substance, in which, however, a faint fibrillation is visible, and in which there are comparatively few elongated nuclei. The lumen is much narrowed, but is lined by a single and even layer of endothelium. Farther back, just behind the lamina cribrosa and where the central artery is still undivided, we have the appearances shown in figs. 5 and 6. The media of the artery is seen not to be thickened, and to show the usual elongated muscle nuclei. Within this a normal elastica is visible, even without special staining, and within this again there is a very considerable thickening of the intima, which narrows the lumen in an eccentric manner. This consists of a somewhat granular but yet faintly fibrillar ground work, in which numerous small dark-staining nuclei are present. The lumen is lined with a single fairly regular layer of nuclei of the same size and staining reaction. It will be noticed that these changes are practically absent on one side, where the artery wall might pass as normal. The central artery contains only here and there a trace of blood. The above condition of endarteritis

persists in all the sections. Weigert's elastic tissue stain shows that there are some fine elastic fibres within the thickened intima.

With regard to the *retinal veins* the most important finding is shown in fig. 4. It occurs in a vein some distance out in the temporal periphery, and represents, I take it, a thrombus beginning to organise. It consists of a large rounded mass whose ground substance is partly homogeneous and partly granular, stains rather deeply with eosin, and shows here and there little groups of red blood corpuscles. There are also scattered groups of nuclei, a few only of which are polymorphonuclear leucocytes. The membrana limitans interna is bowed inwards at the spot, but is intact, and the internal nuclear layer of the retina is bowed outwards and thinned. There is copious hæmorrhage in the surrounding retina. For about two-thirds of its circumference the mass is separated off by a cleft which, however, is crossed by a few trabeculæ. In the remaining one-third there is the appearance of an invasion by young and cellular new-formed tissue. A little to the right there is a small thick-walled artery (out of focus in the figure). These appearances are only to be found in one vein; they are not present elsewhere in the retina. The other veins are much engorged, especially near the disc, and their walls are thickened, but the changes in them are on the whole very moderate. The veins on the papilla are moderately thickened, but slightly behind the base of the physiological cup they form a normal central vein, which continues without abnormality through the lamina cribrosa. Just behind this, however, we have the appearance shown in fig. 5. It will be seen that the circle of the vein is in a general way preserved and is of about the normal size. Its lumen is, however, traversed by a number of trabeculæ, so as to become divided into five loculi each containing blood. These trabeculæ are very thin, are continuous with the tissue of the vein wall, and are always clothed on both sides with a layer of somewhat flattened cells closely resembling endothelium. There is no undue cellular infiltration of the surrounding tissues. This appearance lasts for a few sections and then gives place to the state of things shown in fig. 6. The vein remains of about the same size, but in place of the trabeculæ crossing the lumen there is a little piece of organised

tissue free in the centre. It has a faintly fibrillar structure, and contains a few somewhat elongated nuclei, and in the centre there is again a tiny lumen containing blood corpuscles and lined with endothelium. The outer surface, that towards the main lumen of the vein, is also clothed with an even, single layer of endothelium. The space between this structure and the true vein wall contains a little blood, and the vein wall itself is normal and clothed with a single layer of endothelium. A little vein will be noticed just at this point entering the main vein from the surrounding trabeculæ. The vein now becomes normal and quite patent again. It accompanies the artery for a little way, but begins to part from it unusually soon, leaving only a few small normal venous twigs to accompany it. The vein now passes out towards the periphery of the nerve, and has just reached the pial sheath in the last sections, while the artery still remains in the centre. The vein beyond the point described above shows the ordinary feltwork of elastic fibres in its wall, but there is neither thickening of the wall nor endothelial proliferation.

Optic Nerve.—About the level of the lamina cribrosa, some of the optic nerve bundles show a closer grouping and deeper staining of their nuclei, and there are little wisps of convoluted nerve fibres. This is the condition described by Siegrist* as a pathological change, but proved by Elschnig† to be an artefact and due to the rough handling of removing the globe. The nerve is elsewhere slightly atrophic and unduly cellular. There are some concretions in its sheaths. The direction of the sections in this case makes it difficult to say whether or not there was a glaucomatous cup. If there was, it was at least neither a steep nor a deep one.

The clinical history in this case was not quite typical, inasmuch as both eyes were affected, which is a decidedly unusual circumstance in recorded cases. The left was, however, much more severely involved and showed very copious hæmorrhages, and the disease in this eye was in fact diagnosed by Mr. Snell *intra vitam* as a thrombosis of the

* Siegrist, Arch. f. Aug., vol. xlv, Ergänzungsheft, p. 178.

† Elschnig, Klin. f. Aug., vol. xl, 1902, p. 81.

central vein. It is not improbable that the fits, giddiness, and loss of consciousness described were due to thrombosis in the cerebral vessels, and it is to be noted that after one of these attacks many fresh hæmorrhages were found in the retina. This eye was not interfered with by iridectomy or sclerotomy.

As in Case I, there were no hæmorrhages in the vitreous, though it is possible that the coagulated exudate mentioned may have represented a previous hæmorrhage. The condition of the corneo-iritic angle was much the same in the present case as in the former, but the changes were rather more advanced. It is probable that this corresponded with a longer duration of glaucoma.

That the peculiar appearance shown in fig. 4 represents an organising thrombus, there can, I think, be no doubt. It is of rounded form, it is surrounded by fine connective tissue, it has a small artery in its neighbourhood, and the inner nuclear layer is bowed out at the position which it occupies, just in the manner usual where a large vessel runs in the retina. All these things point to the fact of its being a much distended vein. That the cause of this distension was a thrombus, is shown by the presence of red blood corpuscles among the more homogeneous groundwork. That this thrombus was organising, is shown by the groups of nuclei within its substance and by the invasion from one side of new-formed connective tissue. No other explanation seems feasible. It is too large, rounded, and well-defined to be one of those coagula which are met with in albuminuric and other hæmorrhagic forms of retinitis, usually between the two nuclear layers, but sometimes in the inner layers of the retina. Such coagula were present in this case, but they always showed a squared-off form from lying in the rectangular spaces between the fibres of Müller, nor did they ever show any signs of organisation. It cannot be merely an organising hæmorrhage, for, on the one hand, its boundaries are too definite, and on the other it is surrounded by abundant hæmorrhage, which is evidently not organising.

We must, I think, undoubtedly regard it as a thrombus in a vein within which organisation has begun, but not progressed very far.

With regard to the very unusual appearances shown in figs. 5 and 6, I think the same explanation must be given—that they represent a thrombus, but in this case fully organised and canalised. Indeed, the two appearances give mutual support to this explanation; for if the body in the peripheral retinal vessel is indeed a thrombus commencing to organise, there is nothing strange in finding a more advanced stage of the same process in the central vein. Here, again, it is difficult to think of any other feasible explanation. It is evident that we have not here to do with a division of the vein into branches, for it can be plainly seen in the photograph that these trabeculae (enclosing spaces of such different sizes) are all included within the normal circle of the vein. Further, the appearance is practically the same through several sections, while only a short distance in front of and behind the place shown in figs. 5 and 6, the lumen of the vein is quite normal and single. The little mass in the centre of the lumen in fig. 6 is to be regarded as the transverse section of a pointed process in which the thrombus ended. As a minor confirmatory point, it may be noted that the appearance ceases where a little tributary joins the vein, and it is, of course, well known that thrombi in veins usually extend to the nearest collateral. In Case I there was a true division of the vein a little way behind the lamina, but at no place in the series were the appearances at all like those in the present case. Judging by the different degrees of organisation in the two positions, it is probable that thrombosis occurred first in the central vein and at a later date in the retinal vein. It may be that the central vein was affected at the first loss of vision, and that the retinal vein subsequently became thrombosed about the time when the “large number of fresh hæmorrhages” was noted.

It may be asked, if there was complete organisation of a thrombus in this manner with restoration of the circulation,

why was there no restoration of vision? It must be remembered, however, that the retinal elements would be largely destroyed by the blood already poured out, and would be incapable of recovery. Further, that when glaucoma had occurred (a condition which has been shown to tend to be self-perpetuating), the restoration of the circulation through the central vein would make no difference to the vision, since the seeing elements would still be destroyed by the continued high tension. Evidently when actual adhesions had occurred at the corneo-iritic angle the restoration of the retinal circulation could make no difference to them.

The endarteritis in this case may have been merely part of a general angiosclerosis, when it would, no doubt, to some extent favour the occurrence of the thrombosis in the vein by narrowing the arterial lumen, and so slowing the blood stream, and perhaps interfering with the regulating mechanism. It may also have been wholly or in part secondary to the damming back of the blood caused by the venous obstruction, since obstruction of a vein is known to produce changes in the corresponding artery.

It is noteworthy that in this eye the vein pursued a rather unusual course; it left the artery quite a short distance behind the lamina and curving quickly outwards soon passed out of the nerve. It is possible that this sudden curvature of the vein was the factor which determined the laying down of the thrombus in the position which it occupied, for such a curvature would constitute some hindrance to the return flow of blood, a hindrance which might have been sufficient to cause a thrombus to be deposited on its distal side rather than elsewhere, provided that the general conditions were favourable to the process of thrombosis, and such conditions seem to have obtained in this patient to judge by his history of cerebral attacks. This may also have been the reason why the left eye was attacked rather than the right.

Case III is also chiefly of interest from the pathological aspect. The clinical history from our present point of view

was somewhat defective, inasmuch as the eye was blind and glaucomatous, when first seen, and the media were too opaque to permit of an examination of the fundus. The condition of hæmorrhagic retinitis was, therefore, not diagnosed *intra vitam*.

CASE III.

Martha C., æt. 62, was admitted to the R.L.O.H. on 28.ix.03, under Mr. Tay. The left eye was blind, but how long it had been so was doubtful. It had been painful for 9 days.

V. R. $6/18 \bar{c} + 1 = 6/9$. Tn.

V. L. Hand movements. No. K. P. Fair A. C. Iritis. No view of fundus. T + 2.

The urine contained a trace of albumen. No sugar, sp. gr. 1010.

On 1.x.03 a paracentesis of the anterior chamber was done by Mr. Collins, and again on 5.x.03. On the first of these occasions there was hæmorrhage from the iris.

7.x.03.—Cornea hazy. A. C. good. Iris dull, $1/3$ dilated. Posterior synechiæ T + 2. An iridectomy was therefore performed on 12.x.03, and gave at the time relief from tension and pain.

5.xii.03.—Readmitted. Left painful. Scar bulging. Cornea hazy. K. P. Hyphæma. A. C. shallow above. Outer angles of coloboma drawn up. Lens opaque and swelling. T + 2. V. L. shadows.

The heart was irregular, and there was occasional loud systolic bruit at the apex ? mitral regurgitation.

16.xii.03.—Excision. The eye was hardened in formalin and bisected sagittally.

Macroscopic Examination.—Scar cystoid; hyphæma; lens absent; retina *in situ* covered with hæmorrhages; no hæmorrhage in vitreous; choroid *in situ*.

Microscopic Examination.—Sections were prepared as in the previous cases.

Cornea.—(Edematous spaces are present among the deepest layers of the corneal epithelium. The iridectomy wound is some distance from the corneo-iritic angle. Its two lips are covered with new-formed fibrous tissue, and are not in apposition, the lower lip being in front of the upper. There is much pigment in the

wound which is covered by conjunctiva. To the upper lip of the wound the iris stump is adherent, while the iris from the opposite side has been dragged over and has become adherent to the lower lip. It thus happens that what remains of the anterior chamber is entirely shut off from the wound, which opens direct into the vitreous chamber. The lens had escaped through the wound. For a considerable distance from the edge of the wound there is a layer of new-formed tissue between Bowman's membrane and the epithelium, and in a similar area the superficial layers of the cornea have become cicatricial and vascular, and have lost their even arrangement in layers. Otherwise the corneal stroma is normal.

Corneo-Iritic Angle, Iris, etc.—The iris is adherent to the whole of the ligamentum pectinatum, and for some distance to the back of the cornea. The ligamentum is much condensed, and the space of Fontana are obliterated. There is blood in the anterior chamber. The iridectomy stump is highly atrophic and its vessels are much thickened. The foremost ciliary process is displaced forwards and adherent to it. The iris on the opposite side is somewhat condensed, but shows no vascular change. The ciliary body is much atrophied, especially on the side of the iridectomy. The choroidal vessels are mostly empty, but the choroid seems normal.

Retina.—In addition to the distortion caused by the copious hæmorrhages this case showed definite inflammatory lesions in a few places. The retina is adherent at these spots to the choroid, the pigment epithelium having disappeared, the retina has a more fibrous appearance than normal, and the nuclear layers are greatly distorted. Apart from these patches the nuclear layers are well preserved on the whole. The nerve-fibre and ganglion-cell layers are highly atrophic, and in places oedematous. The hæmorrhages are extensive and are mostly in the inner layers of the retina, but pass through the nuclear layers in places and cause large sub-retinal extravasations. There is also a little blood in the vitreous, but its connection with any of the retinal vessels cannot be traced in the sections. There are no coagula between the nuclear layers. Near the ora serrata the retina is much atrophied, and there is some in-wandering of pigment from the pigment epithelium.

Retinal and Central Vessels.—The *retinal arteries* show but little change. Some of the smaller vessels in the periphery are obliterated, or have their lumen greatly narrowed by a hyaline-looking thickening of their walls, but it is doubtful whether these are arteries or veins. The central artery behind the lamina shows a very considerable endarteritis. It is of the type already described, except that in places the proliferated cells of the intima which compose it have a clear blown-out appearance, not present in the former cases. A specimen stained with Weigert's elastic stain is shown in fig. 11, which represents well the thick (in this case unusually thick) crenated membrane. Within this can be seen a feltwork of curled elastic fibres, fine and coarse, among which there are a few nuclei. The space which separates these fibres from the crenated membrane corresponds to a group of the blown-out looking cells which have just been mentioned, though part of the appearance is perhaps caused by a little obliquity of the section. Where the vein wall is thickened (*vide infra*) the arterial lumen becomes very small.

The *retinal veins* are not greatly engorged. They show considerable thickening, somewhat similar to that shown in fig. 2, but less extensive. There is also less appearance of endothelial proliferation; the lumen is lined by a single layer of endothelium, then comes a clear staining, thick layer with rather scanty but well-stained elongated or oval nuclei. The ground-substance is not hyaline, but finely fibrillated. This layer is sometimes separated from the surrounding tissues by a cleft, but the wall looks shrunken in these places, and it is probably an artefact and not a dilatation of the perivascular lymph spaces as in fig. 2. The central vein is formed by the junction of its branches just in front of the lamina, and at the bottom of the glaucomatous cup. Its wall is at first condensed, but there is no endothelial proliferation or narrowing of the lumen. The connective tissue surrounding the central vessels is here also much condensed. A little further back—toward the posterior part of the lamina cribrosa—the appearance shown in fig. 7 is seen. The surrounding connective tissue is still very dense, and the artery has a good free lumen containing formed blood corpuscles. The vein lumen is relatively small, smaller than that of the artery, but it has still a fair diameter, and there is

no sign of endothelial proliferation. Within the lumen and lying to one side of it there is a rounded homogeneous coagulum, around whose edge there are a number of polymorpho-nuclear leucocytes and a few red corpuscles, while the central area is clear. The remaining part of the lumen contains no blood corpuscles. Tracing the vein backwards, its lumen now becomes narrower, and the coagulum becomes closely plastered up against one wall and more cellular. The lumen now seems to become encroached upon by the neighbouring fibrous tissue, so that it is cut in two, a little lumen being left at one side and a larger at the other. The larger of the two contains a little coagulum. Next we have the appearance shown in fig. 8. The vein is almost entirely replaced by a little knot of loose new-formed fibrous tissue, more cellular than the surrounding connective tissue. There is still, however, some trace of a lumen at each end. The vessel now disappears almost entirely, and its position is only marked by a slightly more cellular area in the connective tissue, without any trace of a lumen. Indeed its proper position could hardly be told from the mere examination of this section, but can easily be located by taking a bearing of the unobliterated and of the obliterated vein from structures which pass uninterruptedly through the series. At this point a moderate-sized collateral appears from the trabeculæ of the optic nerve on the side of the artery *opposite* to the obliterated central vein, and this shortly turns backwards and accompanies the artery by which it is separated from the position of the true central vein (fig. 9). It contains some coagulum similar to that in the central vein before its obliteration, and this coagulum also is shrunken and infiltrated with leucocytes. While this false central vein is still accompanying the artery a small twig enters the tissue in the position of the true vein (fig. 9), and presently the lumen is restored. It is, however, very small, and the vein is extremely thick-walled. Presently the vein which came from the trabeculæ on the opposite side joins with this small lumen, which becomes, therefore, larger, but still not so large as normal (fig. 10). It gradually gets somewhat larger by the accession of fresh collaterals. To the end of the sections (which do not reach the point of exit of the vessels from the nerve) the vein wall

remains enormously thickened. The thickening shows fine wavy fibres in its substance and a few oval nuclei. The vein lumen is clothed with endothelium, and contains no coagulum, but normal blood corpuscles. With Weigert's elastic tissue stain there are only a few very fine curly fibres in the thickening. The main mass of the elastic fibres are outside, where they form a false crenated membrane in the manner already described. Briefly stated, therefore, the changes in the vein amount to obliteration for a space with re-establishment of the lumen where collaterals join it.

Optic Nerve.—There is a deep glaucomatous cup with very steep edges. It reaches almost to the scleral ring in one direction, leaving only the thinnest possible layer of tissue, from which all trace of emerging nerve fibres seems to have disappeared. There is some hæmorrhage within the cup. The lamina itself forms a meshwork from which practically all the nerve fibres have disappeared. Further back in the nerve the atrophy is very extreme. The nerve is extremely shrunken, the trabeculæ are thickened, and it looks unduly cellular. Two nearly opposite sectors, however, are especially marked out by the extreme degree of the atrophy which they present. No nerve fibres at all are to be seen within the trabeculæ. The two sectors together take up about one-third of the nerve. They correspond perhaps to the places where the nerve fibres were most severely nipped in crossing over the edge of the cup, but I could not with certainty trace this relationship, because the arrangement into sectors becomes less definite near the lamina.

The pathological changes in the anterior half of this globe are not of much importance to the present inquiry, because the eye had been interfered with by iridectomy 2 months before it came to excision, and, therefore, it is impossible to say with regard to some of the changes whether they were due to the disease itself or secondary to the operation. It may simply be stated that the blocking of the corneo-iritic angle was much more complete than in Cases I and II.

In this case there was hæmorrhage into the vitreous,

but, of course, in an eye which had been subjected to an iridectomy, and which was not excised for nearly 3 months after the onset of glaucoma, it is impossible to say when the vitreous hæmorrhage occurred and what relation it may have had to the causation of the glaucoma. The deep cupping of the disc in this case was a sign of the long continuance of the glaucoma, and so probably was the extreme atrophy of the nerve.

With regard to the retinal changes it may be noted that whereas in Cases I and II there were no signs of retinal inflammation, but only of that distortion of the retinal elements by the out-poured blood which usually goes under the name of hæmorrhagic "retinitis"; in the present instance there were signs of true inflammation in the patches of fibrosis mentioned above.

The chief interest of the case, however, lies in the condition of the central vein. Following it backwards we have first a normal lumen, then an area of complete obliteration, then, after it has been joined by collaterals, a space in which the lumen reappears, but is greatly narrowed by an enormous thickening of the vein wall. The coagulum I believe to be merely a *post-mortem* clot, or, at least, to have been deposited from completely stagnant blood; it shows neither the lamination of a thrombus deposited from flowing blood nor the organisation which one would expect in a thrombus of some duration. The slight infiltration of its edge with leucocytes might quite well, I think, have occurred in the time between the molar and the molecular death of the tissues. Further, similar appearances were present in some of the ciliary arteries. I have already spoken of a similar appearance, described and figured by Michel as a "thrombosis" of the central vein, in one of his cases. The appearance which succeeds this in following the vein backwards is, however, evidently quite a different thing. The vein becomes entirely replaced by a little knot of connective tissue not very different from the surrounding connective tissues, but easily enough distinguished by its

greater cellularity, and this little knot can be readily proved to be in the exact position of the vein by its relation to surrounding structures, which run unaltered through the series. Besides, there is for a space no other vein accompanying the artery which could be the central vein proper (fig. 8). There can, I think, be no doubt that this is an organised thrombus which has failed to canalise as in the last case, but has gone on to complete obliteration. That it is not merely an obliteration by endothelial proliferation is shown by a high power examination of its structure, which shows it to be made up not of thick-walled vein, but of young connective tissue. Its extreme shrunkness, indeed, is almost sufficient of itself to prove the fact. It was not possible in this case definitely to state that the collaterals in the trabeculæ of the nerve corresponding to the obliterated portion of vein were enlarged, but this is hardly to be wondered at, for these collaterals are many and the blood would be distributed among them all, so that each one would be but little more engorged than normal. The extensive retinal hæmorrhages show that the collaterals were not efficient for the carrying off of the dammed back blood.

With regard to the great thickening of the vein wall central to the obliterated portion, its significance is not quite certain. It may be that it was present before and helped in the determination of the thrombosis, or it may be that the meagre blood stream and collapsed condition of the vessel after the occurrence of the obstruction in some way helped to cause the thickening of the wall. At any rate, it is remarkable that the vein should be so very thick central to the obstruction and so relatively thin on the bulbar side. The extreme atrophy of the optic nerve is to be attributed to the long duration of glaucoma and the depth of the cupping.

Case IV is very similar to the last and may be more briefly reported. Mr. Flemming, under whose care the patient was, has kindly supplied the clinical notes.

CASE IV.

"Mr. B., æt. 59, was first seen 11.xi.03. The right eye had been failing gradually. V = hand movements. O.E. Much retinal œdema, and numerous hæmorrhages in the nerve-fibre layer for the most part. Nasal border of optic disc obscured by the swollen retina. Veins very engorged and tortuous. Arteries are hidden by the swollen retina, and are only to be made out here and there.

Urine sp. g. 1.012. Trace of albumen; no sugar. Arteries rigid, but no organic cardiac disease.

19.xii.03. Eye painful; tension +2; cornea hazy; pupil small; no p.l.

23.xii.03. T + 3. Eye excised; much bleeding in attempting to divide the nerve long. Much bleeding at two subsequent dressings, requiring the orbit to be plugged." A portion of the very long nerve which Mr. Flemming had secured was unfortunately lost, so that the sections do not extend beyond the point of entrance of the vessels. The eye was preserved in formalin, and bisected horizontally.

Macroscopic Examination.—The corneo-iritic angle looked only a little blocked. There was no blood in the anterior chamber nor in the vitreous. A large mass of exudation hid the situation of the disc, and from within it the obviously enlarged and tortuous veins appeared. It caused a swelling of about 1 mm. Large hæmorrhages were present in every part of the retina, and a few white plaques.

Microscopic Examination. Cornea, Sclera, etc.—A few vesicles in the corneal epithelium. Stroma normal. Limbus and episcleral vessels moderately infiltrated. Sclera normal.

Corneo-Iritic Angle.—This is blocked by adhesion of the root of the iris to the ligamentum pectinatum, usually for about half its extent, though in places the adhesion reaches as far as the membrane of Descemet. Where the adhesion is most extensive there is a certain amount of condensation of the ligamentum, with obliteration of the spaces of Fontana, but on the whole this is moderate, and in some sections but little marked. There are a few small blood extravasations in the root of the iris, and in the spaces of Fontana.

Iris, Ciliary Body, and Choroid.—The iris stroma is normal, and the vessels only moderately thick walled. The ciliary body is normal. The choroidal vessels are mostly empty and collapsed, so that the choroid looks thin. There are a few hyaline outgrowths of the membrane of Bruch.

Retina.—The retina contains some very large hæmorrhages near the disc, and in this situation the retinal layers are much distorted and their nuclei widely scattered. The remainder of the retina is infiltrated in every part with blood, but none of the hæmorrhages are very large, and the nuclear layers are tolerably distinctly preserved. As is usual, the hæmorrhage is most abundant in the nerve-fibre and ganglion-cell layers, but it has permeated all the layers in places, and there are both pre-retinal and sub-retinal hæmorrhages. A few homogeneous coagula are present between the nuclear layers. There is a moderate amount of vacuolation near the ora serrata, and there are some nuclei among the rods and cones.

Retinal and Central Vessels.—Some of the smaller vessels in the periphery show a true hyaline change. They have a glistening, homogeneous aspect, involving the whole wall, and show no nuclear staining. Whether these are arteries or veins is uncertain. The changes sometimes amount to obliteration. The *retinal veins* are moderately engorged. They show a considerable thickening of their walls, which is fibrillar, and contains well-stained spindle-shaped nuclei. The endothelium seems not to be proliferated, and the thickening is apparently confined to the connective tissue wall. It does not look hyaline. The central vein is formed just in front of the lamina, and here it is much distended with homogeneous coagulum and well-formed red blood corpuscles. A few sections further back, but still within the lamina cribrosa, the vein suddenly disappears, and there is no vein at all accompanying the artery, unless a little slit in the connective tissue at one side represents it (fig. 12). This slit, however, is not lined by any regular endothelium, and its wall consists of connective tissue entirely similar to the connective tissue around, so that it is probably merely an accidental cleft in the tissues, perhaps caused in the preparing of the sections. The surrounding connective tissues show no undue cellular infiltration. There are many much

engorged collateral branches in the surrounding nerve trabeculæ in the area within which the vein has disappeared. The exact manner of the disappearance of the vein can unfortunately not be demonstrated in this case as it was in the last, for only every fourth section in the series was mounted. In one section the vein was present and distended, in the next it was absent, as is shown in fig. 12. In the section following, two very small veins appear in the position formerly occupied by the main vein, and these presently join together (fig. 13) to form a larger, but still very small, central vein. These two veins contain well-formed red blood corpuscles. Following the vein backwards, it is found to receive many small and large collaterals from the surrounding trabeculæ, by the accession of which it gradually resumes its normal size and remains normal in size to the end of the series (fig. 14).

The retinal arteries are much thickened, and in places nearly obliterated. The thickening is cellular, and suggests endothelial proliferation. In front of, and within the lamina, the artery is much distended by homogeneous coagulum with leucocytes in the periphery and red blood corpuscles in the centre. This coagulum has sometimes shrunk and pulled away the intima of the vessel, evidently a *post-mortem* appearance (fig. 13). There is at this point no endarteritis, but in following the artery back thickening of the intima gradually appears, until finally, where the vein reattains its normal size, the arterial lumen has become smaller than the venous. Next, the formed red corpuscles within the lumen begin to be replaced by homogeneous coagulum, in which there are a few leucocytes, and a little farther back these leucocytes are replaced by elongated cells, the groundwork being still homogeneous. The lumen now becomes filled with an organised mass, the substance of which is composed of coiled-up wisps of fine fibres, among which spindle-shaped nuclei are visible (fig. 14). There are no capillary vessels within it. The mass is separated from the vessel wall by a cleft which is complete all round, and not bridged in any of the sections (every fourth), and within this cleft there are a few red blood corpuscles. There is much endarteritis at this point. This appearance lasts for a few sections, and is then replaced by more homogeneous coagulum with elongated nuclei, and finally by normal red blood corpuscles. The endarteritis becomes less from this point to the end of the series.

Optic Nerve.—There is no glaucomatous cupping. The nerve itself is moderately atrophic and unduly cellular. There are some concretions in the arachnoid sheath.

This case shows many points of resemblance to the last. Clinically it differed, inasmuch as the diagnosis of thrombosis of the central vein was made *intra vitam*, and the hæmorrhagic retinitis was therefore definitely known to have preceded the glaucoma. The blocking of the corneo-iridic angle was moderate, both in extent and in degree, and the spaces of Fontana seemed to be left fairly free for drainage. The retinal changes were entirely those of distortion from extravasated blood; there were no inflammatory infiltrates. The retinal vessel changes were those of proliferation and degeneration; there were no thromboses within the lamina cribrosa.

The disappearance of a certain length of the central vein, without leaving a trace, is certainly a noteworthy fact. We have presumably the same changes as in Case III, but they have gone a step farther, and the new-formed connective tissue has totally cicatrised and become indistinguishable from the surrounding tissues. Were it not for the findings in the last case, by which we can trace the process of cicatrisation, we might almost be tempted to believe that we had to do here with a congenital peculiarity—that a portion of the vein was congenitally absent, and that its place was taken by enlarged collaterals among the nerve. That, however, is a condition which, so far as I know, has never been described. It is to be remembered that we are not dealing with an early division of the vein, for, both in front of and behind the obliterated portion, it has a normal lumen. Then again, we have seen, in the last case, the vein *almost* disappear, its position being only marked by a little cellular infiltration. Further, we have to remember that obliteration of the vein accounts for the clinical symptoms of venous obstruction, which are not otherwise accounted for by anything in the pathological examination. So that

there seems to be sufficient proof that we really have here a pathological lesion which has affected a smaller length of the vessel than in Case III, and whose stages, therefore, cannot be so exactly followed.

With regard to the little cellular plug in the artery, there can, I think, be little doubt that it is an organised thrombus, and that the thrombosis in the artery was secondary to the interference with the blood flow, caused by the occlusion of the vein. In the first place, the changes in it are not so advanced as those which have obliterated the vein, and, therefore, it is presumably younger. Then again, if the arterial plugging were the primary lesion, the venous obstruction and hæmorrhages seen with the ophthalmoscope would be totally inexplicable. The symptoms were at no time those of thrombosis of the central artery, a lesion which has been several times proved to give the picture of "embolism" of the central artery, and which is, in fact, probably at the root of most, if not all, of those cases of so-called "embolism." That it is an organised plug, foreign to the vessel, and not an endarteritis, which has gone on to complete obliteration, is evident at a glance, from the histological difference between the mass in question and the endarteritis, which is also present. Besides, there is quite a definite cleft between the two containing blood. It is certainly somewhat difficult to account for the fact that this cleft is complete all round, and that nowhere in the sections is it bridged over by connective tissue, for it is evident that the process of organisation, which is essentially a reaction of the surrounding tissues, cannot but result in the intimate union of the plug in the lumen and of the tissues in the vein wall. It may be that there *is* a connection with the vessel wall somewhere, but not in the present series, which includes only every 4th section; or again, this may be a form of canalisation in which the clot itself is not channelled (as in Case II), but in which the blood has found its way by the side of the thrombus, and, aided by the shrinkage of the new-formed connective tissue, has finally

succeeded in making a cleft between it and the vessel wall right round. It might be argued that the presence of a complete cleft proves that the plug is really an embolus, *i.e.*, that a fibrous mass formed elsewhere in the vascular system had become detached and swept into its present position, and that the reaction of the surrounding tissues had not yet commenced. But, if so, whence did it come in the present instance, and how can it be fitted into the history of the case? It would be necessary to regard its presence as a mere coincidence, which seems a very unlikely supposition.

The most probable view of the sequence of events here, then, seems to be that there first occurred a thrombosis of the central vein at its narrowest part, where it passes through the lamina. The general arteriosclerosis and the nephritis present in the case very probably bore a part in causing it. This thrombus became organised in the ordinary way, but failed to canalise, and sufficient time elapsed for the new-formed connective tissue to totally cicatrise and disappear. In the meantime (at what stage exactly must be uncertain), the hindrance to the circulation caused by this occlusion reacted on the blood flow in the artery, and, at a point where the lumen was already narrow from endarteritis, a thrombus occurred, and in its turn also organised. It is not likely that any change would be brought about in the clinical symptoms by this occurrence, for the retina would already be the seat of an intense hæmorrhagic retinitis from the venous plugging, and the plugging of the artery, in addition, would make but little difference. The next stage may have been, as argued above, an imperfect channelling between the thrombus and the artery wall, which resulted in some degree of restoration of the arterial current, and caused the separation of the thrombus from the wall by a narrow cleft.

Four cases have now been given in which the appearances known clinically as "thrombosis of the central vein" were either seen ophthalmoscopically *intra vitam*, or were found macroscopically when the eyes were bisected after hardening

Of these, three showed evidence that there had really been a thrombus to account for the symptoms, and the successive stages in the processes of thrombosis and organisation may be roughly indicated by figs. 4, 5, 8, and 12. It has been already pointed out that some uncertainty remains with regard to Case I, because the optic nerve entrance was cut longitudinally, for it will be readily understood how little could have been said with certainty of the changes shown in figs. 7 to 11 (for instance) if the sections had passed longitudinally to the nerve entrance in the usual manner instead of transversely. The number of my cases is still too small, but they lend support to the belief that if some of the other cases in the literature had been treated in the same manner, more definite results might in some instances have been obtained, and the disease in question given a firmer and more consistent pathological basis. One may hope that more records of pathological examinations of these cases may be published.

It remains now to discuss certain problems raised by cases of this sort, and to see how far they are illustrated by the cases described. The chief of these problems may be briefly stated as follows: (1) What general and local conditions favour the occurrence of thrombosis of the central vein? (2) Why does glaucoma so commonly follow in these cases? (3) What is the exact nature of the changes found in the central and retinal vessels, and how much of them is primary and how much secondary to the onset of thrombosis and glaucoma?

Chief among the causes of thrombosis of the central vein must undoubtedly be counted angiosclerosis, including in this term all those conditions which tend to the thickening of vessel walls and the narrowing of their lumina, and including affections both of arteries and of veins. An examination of the literature shows that out of 26 cases arteriosclerosis of the systemic vessels was present in 11, absent in 8, and not mentioned in 7. Schoenewald* found

* Schoenewald, quoted in Nagel's *Jahresbericht*, 1900, p. 620.

arteriosclerosis present in 7 out of 18 cases. In 9 cases personally observed it was present in 4 and absent in 5. These figures do not give so large a proportion with arteriosclerosis as might have been expected from some of the descriptions of the disease, in which rigidity of the radial and temporal arteries is stated to be nearly always present. It may be noticed in passing, that while arteriosclerosis of the peripheral vessels is a valuable guide pointing to the probability of arteriosclerosis being present in the vessels of the eye, its absence cannot be taken to mean absence of vessel change within the eye-ball. In Case I, for instance, in which the changes in the retinal vessels reached the very high degree shown in fig. 2, there was no evidence of arteriosclerosis in the peripheral vessels, and I have seen this also in another case, which I had the opportunity of examining microscopically. The same thing is well-known to obtain in the case of the cerebral vessels, which are sometimes highly sclerosed, although no evidence of general arteriosclerosis is furnished by the peripheral arteries. There may even be extensive microscopic changes in the retinal arteries without ophthalmoscopic evidence as Hertel* has recently shown. It is, however, true that in nearly all the cases of thrombosis of the central vein which have come to microscopic examination the vessels have been found extensively diseased. It was certainly so in all four of my own cases, and in two others of which I made a partial examination.

It follows that if angiosclerosis be a cause of thrombosis, the conditions which favour the occurrence of angiosclerosis must also be included among the causes of thrombosis. Of these the chief are old age, heavy strains, nephritis, and perhaps syphilis.

The influence of old age is best represented in tabular form, as follows:—

* Hertel, *Arch. f. Ophth.*, vol. lii, pt. 2, p. 191.

Age.	Cases from literature.	Personal observations.
1—20	1	—
20—40	5	2
40—60	8	6
60—80	10	1
80—90	1	—

The figures of Ammann* may also be quoted, who found among 60,000 patients in Haab's clinique 20 cases of thrombosis of the main venous stem, of whom 15 were between the ages of 50 and 80, and 2 of the others, æt. 47 and 29 respectively, had heart disease and arterio-sclerosis. These figures are sufficient to show how the disease increases with increasing age, a fact which is of common experience. Nearly all the cases occurring under 40 are of an unusual type, and in some of them the diagnosis is doubtful.

Ammann has especially called attention to the frequency with which those suffering from thrombosis of the central vein are persons accustomed to much toil, and especially to much stooping. He found that 13 out of his 20 cases were either peasants or persons who did gardening for pleasure, while 2 others were smiths. We have here perhaps both a remote and an immediate cause of the affection, since constantly repeatedly strains would tend to cause angio-sclerosis, while the venous congestion caused by some especially violent strain might be the cause of the actual thrombosis. It is because of their greater liability to physical strains, Ammann believes that more cases occur among men than among women. My own experience has given 4 cases in males and 5 in females, but this is probably a coincidence, since it is undoubted that men considerably predominate in the reported cases (16 to 8).

With regard to the influence of nephritis, it will be found that this is less prominent than might have been expected. Out of 26 recorded cases it is only mentioned

* Ammann, Deutschmann's Beiträge, Heft. xxxviii, 1899, Heft. xxxiii, p. 1.

5 times, in 5 it is not noted whether it was present or absent, and in 16 it was not present. Among my own cases it was present 4 times, absent twice, and not noted twice, so that it was present in a much larger proportion than in the cases in the literature. In any case it is to be regarded not as a direct, but as an indirect cause, it will act presumably merely by helping in the causation of angiosclerosis. Syphilis is usually credited with having a considerable influence in the etiology of angiosclerosis, *vide* the frequent history which one obtains of it in cases of aneurism. Yet it is very seldom mentioned in the reports of cases of thrombosis of the central vein, and I have only met with one case personally in which a clear history of it was obtained.

Angiosclerosis, then, may be given the first place in causing thrombosis of the central vein. Yet all cases do not seem to be so explained, and among other causes valvular heart disease must be mentioned. I may very briefly quote the following case in illustration.

Margaret M, æt. 25, had noticed a dimness in the sight of the left eye a fortnight before she presented herself for examination. She had suffered since early childhood from "heart disease," of which the origin was obscure, since there was no history of acute rheumatism or of chorea. She had long been liable to be laid up at times with attacks of cardiac insufficiency, and this had happened 3 months before she was first seen. Loss of vision was sudden, without any prodromal phosphenes, etc., and in the form of a uniform grey veil before the eye. She was at the time in her usual impaired health—not confined to bed.

The patient was very breathless and cyanosed, and had some œdema of the ankles. The heart's action was very "tumultuous" and irregular; there was pre-systolic thrill, and a rough murmur preceding and running into the first sound of the heart. The diagnosis with regard to the cardiac condition was "mitral stenosis with cardiac insufficiency."

V.R., 6/6 and J1. O.E. normal.

V.L. Shadows. O.E. The fundus strewn in every direction

with large hæmorrhages, striate, round and irregular, with here and there among them, yellow patches. The disc was encroached on by hæmorrhages from all sides. The arteries were hardly visible, the veins much swollen, very dark and tortuous; in fact the typical picture of thrombosis of the central vein.

There seemed to be no other cause for the occurrence of a thrombosis in this instance than the interference with the venous circulation brought about by the mitral stenosis. The patient was too young to make it probable that she had angiosclerosis, even in the presence of valvular heart disease, and there was certainly no proof of it in the peripheral vessels. A somewhat similar case of Juler's has been already mentioned. Valvular disease has also been present in some of the other cases in the literature (*vide* Michel's Case I, Türk's, Meyerhof's), but either associated with evident arteriosclerosis, or occurring at an age when arteriosclerosis might be expected to be present. Schoenewald gives 3 cases out of his 18 as suffering from heart disease.

It might be expected that weakening illnesses might occasionally be followed by a thrombosis of a marantic nature, but it seems that this is seldom the case. The patients are usually apparently in their ordinary health. I have, however, in 3 cases obtained a history of influenza, a disease which is known sometimes to cause thrombosis in the cerebral vessels. In two of them dimness of vision occurred during convalescence, and in one about a month after an attack. I should not, however, be inclined to lay too much stress on the influenza as a causative factor, for the patients were not in any of the instances reduced to any very profound state of debility. To a similar category may be referred the case of Würdemann, in which thrombosis of the central vein followed a fortnight after an attack of mumps in a boy of 8. Also possibly marantic was Case II of Michel's mentioned in the table, in which a thrombus was found in the central vein of a patient who died of leukæmia, and a case of Ballaban's* (not proved pathologically) in a

* Ballaban, Arch. f. Augenh., vol. xli, p. 280, 1900.

girl suffering chlorosis. Goh's case may also be mentioned here, in which a hæmorrhagic retinitis appeared 3 days before death from septicæmia, and in which a thrombus was found in the right central vein. It is a noteworthy point (first mentioned by Michel) that in not a few cases dimness of vision has been first noticed on awakening in the morning. This was the history in the cases of Bankwitz and Wagenmann (Case I), and I have myself obtained it in 3 out of 9 cases. It probably merely signifies that, given conditions favourable to the occurrence of thrombosis (angiosclerosis, etc.), the lowered blood pressure and slower current during the hours of sleep are likely to put the finishing touch to the process.

A case reported by Eversbusch* may be merely mentioned, in which thrombosis of the central vein was supposed to have followed an injury with fracture of the upper jaw, nasal, and sphenoid bones. It is a very doubtful case (possibly of abruption of the optic nerve), not pathologically examined, and at any rate not of interest to the present inquiry. A few rare cases in which thrombosis is said to have followed upon orbital cellulitis may also be passed over as not bearing on present problems.

Among strictly local conditions favourable to, but not necessarily by themselves, causing thrombosis of the central vein, may be mentioned an unusual course of the vein itself, since it is evident that the more curved or tortuous the tube is along which the blood flows, the greater will be the friction, the greater the slowing, and the more the liability to thrombosis if the wall be diseased. There is a certain amount of proof that these considerations are of some little importance. Goh believed that in his case a thrombosis occurred in one eye and not in the other because the vein on that side took an unusually great curvature, and it will be noticed that in Case II, reported above, the vein just central to the thrombosed part took an unusual course, curving sharply away from the artery to reach the periphery of the nerve.

When all the above causes have had due weight, there

* Eversbusch, *Klin. Monatsbl. f. Augenh.*, 1899, p. 1.

still remain certain cases not easily explained. These are the cases occurring in young people without cardiac or renal disease. The cases of Purtscher and Weinbaum may be especially mentioned, which occurred in patients *æt.* 21 and 25 respectively, and without heart disease, arteriosclerosis, or nephritis. I have also seen a similar case in a young lady, which was further remarkable in that the hæmorrhage subsequently entirely disappeared and the vision rose to 6/6, a thing which I have not seen in any other case of true thrombosis of the main stem of the vein. These cases are not easy to account for since thrombosis in any vein is uncommon in the young, except in the two instances of varicose veins and the uterine veins after parturition, in both of which instances there are special circumstances not to be found in the central vein of the retina. Angelucci speaks of two forms of thrombosis—the marantic found in old people with angiosclerosis, and the phlebitic found in young people; but, as we have seen, Angelucci's own cases are open to the gravest suspicion as to whether they were really instances of thrombosis of the central vein, and further, his statements rest on no pathological proof. Nor is it much easier to account for a primary phlebitis in young people than to account for angiosclerotic changes. Such cases are especially worthy of pathological research as opportunity offers.

Turning now to the question why glaucoma should follow on these cases of intense hæmorrhagic retinitis, we find several explanations of the fact put forward. That glaucoma does follow oftener than can be explained on the ground of mere coincidence is a well-ascertained fact. So long ago as 1869, before thrombosis of the central vein had been described as such, v. Graefe* gave his experiences on this point, and stated that, from the number of cases in which he had seen this sequence of events, he could not regard the occurrence of glaucoma as accidental. One explanation which has been

* v. Graefe, *Arch. f. Ophth.*, vol. xv, 1869, pt. 3, p. 184.

put forward, chiefly by Wagenmann, is that the two phenomena, hæmorrhagic retinitis and glaucoma, are really independent of one another, but are both dependent on a common cause, viz., arteriosclerosis, *i.e.*, that the vascular changes which in the posterior half of the eye resulted in hæmorrhages, in the anterior half of the eye resulted in impaired drainage and glaucoma. A little consideration of this theory will, I think, show that it is untenable. If the glaucoma is not directly dependent in some way on the hæmorrhagic retinitis, why should it attack the eye affected with hæmorrhagic retinitis rather than the other, as it undoubtedly does? v. Graefe observed 22 cases in which glaucoma followed upon hæmorrhagic retinitis. In 10 of these the other eye was unaffected after a lapse of 2 years. In 6 glaucoma followed in the other eye, but was in each case preceded by retinal hæmorrhages. In 5 the other eye was subsequently affected with hæmorrhagic retinitis, but remained free from glaucoma, and in 1 both eyes were simultaneously attacked. Presumably, on an average the amount of angiosclerosis in one eye will be much the same as in the other eye of the same person, and if the glaucoma is not dependent on the retinal hæmorrhages, but on angiosclerosis, there seems to be no reason why it should fall with greater frequency on the eye affected with retinal hæmorrhages than on the one not so affected, but the above figures show that there is no tendency for the other eye to become glaucomatous, except in consequence of the occurrence of retinal hæmorrhage in it. Again, the hypothesis that both are due to the common cause angiosclerosis does not explain cases such as those of Weinbaum, Purtscher and Wurdemann, in which hæmorrhagic retinitis followed by glaucoma occurred in young patients, since in these cases the glaucoma cannot have been due to angiosclerosis, and must undoubtedly be looked upon as a sequel to the retinal hæmorrhages. We may then fairly conclude that the two conditions are not independent, but that the glaucoma is directly the consequence on the retinal affection.

In a few cases there has been evidence of iritis (Wagenmann, Case III, Ganthier, etc.), and where this has occurred there would, of course, be an increased tendency to glaucoma, but that this is any usual explanation of these cases is easily negatived by most of the clinical histories. In Case I, given above, which was closely followed from first to last, there never was any trace of iritis. Further, it is distinctly uncommon to find any trace of inflammation in the stroma of the iris microscopically.

There are also certain instances in which glaucoma has followed upon the use of atropine (Deutschmann), but this also is quite an exceptional history in these cases, and probably indicates that the eye was already predisposed to become glaucomatous, and that the use of atropine, as it were, merely tipped the balance.

There seems then to be sufficient proof that in the majority of instances the association of glaucoma with hæmorrhagic retinitis is not a coincidence, that it is not merely a case of both being due to arteriosclerosis, but in reality independent of one another, and that it is not due in most cases to such accidents as the use of atropine or the intercurrent of iritis. We must conclude, therefore, that in some way the glaucoma is directly caused by the preceding retinal hæmorrhages. It has been supposed that in these cases there has always been a rupture of the blood through the limitans interna into the vitreous. In consequence of this, it is thought, the lens may be carried forward, bearing with it the iris and narrowing the corneo iritic angle. At the same time the nature of the fluid drained off at this angle will be altered; it will become more colloidal from admixture with the proteid constituents of the blood, and will, therefore, be less easily able to pass through the spaces of Fontana, and these two factors combined will result in increased intra-ocular tension. Some support is lent to this explanation by the fact that in many instances, with the onset of glaucoma, the media become too opaque to be illuminated, and it is also undoubtedly true that blood has actually been found in the

vitreous in some of these cases. It was present in Case III, and probably in Case II, reported above. No doubt it is the case that the presence of blood in the vitreous will increase the tendency to glaucoma, but it is quite certain that glaucoma may also occur without any trace of such vitreous hæmorrhage. In Case I, for instance, there was certainly no blood in the vitreous 9 days before the eye was obtained, and none was found on bisecting it after excision, so that it may fairly be assumed that none had occurred, and the opacity of the media in this case must be attributed mostly to cedema of the cornea.

It is, however, possible that, without actual hæmorrhage into the vitreous, the lymph currents drained at the corneo-iridic angle may still be altered in the manner indicated by the presence of profuse retinal hæmorrhages and retinal venous obstruction. It is to be remembered that the canal of Stilling is capable of being injected from the lymph spaces around the central vessels (Leber*), which shows that venous (and therefore lymphatic) obstruction in the nerve may alter the constitution of the lymph currents in the vitreous.

Such an alteration in the lymph currents may be the explanation of the onset of glaucoma in these cases, but is not the full explanation of its continuance. We have not merely to do with the drainage of abnormal lymph through normal passages, for already on the seventh day, as we see in Case I, there is a certain amount of blockage of the corneo-iridic angle by fibrous tissue—the apposition has become an adhesion—and this is a condition which constantly increases the longer the glaucoma persists. It is to be remembered also that glaucoma does not follow in every case of thrombosis of the central vein. I know of one case (shown me by Mr. Hancock) in which repeated vitreous hæmorrhages have occurred under observation, which has yet lasted 3 years without the occurrence of glaucoma. So that possibly the imperfectly understood factors which predispose to ordinary

* Leber, Graefe Saemisch Handbuch, 2nd edit., pt. 1, vol. ii, chap. XI, p. 84.

primary glaucoma play a part, *e.g.*, general smallness of the eye, shallowness of the anterior chamber, relative largeness of the lens, and angiosclerosis. It is to be remarked, however, that in Case I the anterior chamber was not shallow, but rather deep, though whether that is a common condition in cases of this kind I do not know. Angiosclerosis is probably an important factor in these cases, not as an independent cause of glaucoma according to Wagenmann's explanation, but as the predisposing cause which makes the drainage fail when the abnormally constituted lymph attempts to pass through the filtration angle.

We come now to the difficult question, What is the nature of the changes in the vessels described and figured in the foregoing account? Are they all of one kind, the different appearances being different stages in one process, or is there more than one kind of pathological change which the central vessels may suffer? Further, are the changes in the arteries of the same nature as the changes in the veins? In the first place, a few words may be said as to the peculiarities in structure of the central vessels and their retinal branches, and more particularly as to the elastic tissue in their walls, since the staining of this elastic tissue by special methods, and especially by Weigert's elastic tissue stain, has given much information recently both with regard to the normal structure of the vessel walls and with regard to the seat of pathological changes in them. It has also been of much service in distinguishing, in the case of the retinal vessels, which are arteries and which veins, a distinction by no means easily made when they are pathologically altered. The central artery, then, as far as the lamina, has the normal structure of a small arterial twig—an endothelial lining, a very narrow sub-endothelial layer, a well-marked crenated *elastica interna*, a relatively thick muscular coat with scanty elastic fibres, and a connective tissue *adventitia* fading indefinitely into the surrounding connective tissues, and containing an abundance of irregularly disposed fine elastic fibres. So far, there is nothing peculiar, but, just as the

artery passes through the lamina cribrosa, there is a change. There ceases to be any definite single crenated membrane, and its place is taken by an entanglement of fine elastic fibres, which still separates media from endothelium. Following the arteries further into the periphery of the retina, this elastic tissue soon becomes less, and in the smallest twigs seems to disappear. The wall of the central vein is composed almost entirely of fine connective tissue, only a very few cells being present, which resemble muscle cells. This fibrous tissue has no clear outer boundary, but shades off into the surrounding connective tissue quite indefinitely. It contains tolerably abundant irregularly disposed elastic fibres, which are very variable in amount, and apparently increase, as Hertel has shown, with advancing age. Sometimes these are so abundant, and so regularly arranged in a transverse direction, as to simulate a crenated membrane, more especially when the vein is collapsed and thrown into folds, but I have never been able to persuade myself of the existence of a true membrane in the vein like the crenated membrane of the artery; the high power always shows that we are really dealing with a close feltwork of fine fibres, an appearance which is not given with any power by the true crenated membrane of the artery. The distinction between intima and media is, therefore, much less distinct in the vein than in the artery, indeed, the intima seems to consist of little more than the endothelium, with, perhaps, a little sub-endothelial tissue. On reaching the lamina cribrosa, the elastic tissue of the vein wall blends with the elastic tissue of which the lamina is mainly composed; and within the lamina, so far as I have observed, there is no elastic tissue in the vein wall, and we have, therefore, in Weigert's elastic tissue stain a valuable means of distinguishing artery from vein, when the ordinary means—the wider calibre, extreme thinness, and lack of muscular tissue in the wall—fail us in consequence of pathological changes. It is well known, of course, that there is no muscular tissue in the walls of the

retinal veins. I believe that the above will be found universally true, but my observations are still somewhat scanty, and more research is needed finally to establish some of the points.

Turning now to the present series of cases we have not much difficulty in defining the seat of the pathological change in the arteries. A glance at fig. 5 will show, even without Weigert's special stain, that the intima is the part affected, and since the lumen is still lined with a tolerably even layer of endothelium it is probable that the seat of change is the sub-endothelial tissues, though it is not entirely excluded that the endothelium itself may have become proliferated while still presenting an even layer to the lumen. Weigert's elastic stain shows this even more clearly by defining the *elastica interna* (fig. 11), and further shows that among the proliferated cells there are numerous very fine elastic fibres which form imperfect crenated membranes within the true one, reaching each a part of the way round the lumen, but none entirely round. Within the lamina cribrosa the changes in the arteries are similar. They affect the intima (fig. 1), and seem to consist chiefly of proliferation of the endothelium.

In Case I the changes in the central vein are also undoubtedly in the intima (fig. 3). They are in the form of a clear-looking ground worked with scanty oval nuclei, and are within the area of the curly elastic fibres of the media and adventitia. Changes such as are shown in Case III (fig. 10), however, seem to involve also the connective tissue wall of the vein. The thickening is very great, there is a certain faint fibrillation in the groundwork, and Weigert's elastic tissue stain shows a very few faint elastic fibres. The endothelium shows but slight sign of proliferation. The changes in the retinal veins are probably usually of this kind. For instance, in the vessel shown in fig. 2, which has already been shown to be a vein, we have probably both endothelial proliferation and thickening of the connective tissue wall.

The terms "hyaline thickening" and "hyaline degeneration" have apparently been used somewhat loosely by authors to represent any thickening of the retinal vessel walls of more or less homogeneous aspect. They should, I think, be used only for those cases in which there is evidence of molecular impaired vitality in the tissues, in the form of loss of fibrillar structure in connective tissues, and of lost or much impaired nuclear staining. On this standard none of the changes just spoken of should be termed "hyaline degeneration," for in spite of the somewhat homogeneous ground substance in some instances (fig. 3), the nuclear staining is well preserved. "Fibrosis" would be a more proper term for the changes shown in fig. 3, and they are no doubt to be looked upon as a preservative tissue reaction against abnormal circumstances in the circulation, a strengthening of the vessel wall against undue strains. Some of the vessels in these sections do, however, show a change different from the above. They are mostly small vessels, have a homogeneous glistening aspect, and show no, or very scanty, nuclear staining. To these the term "hyaline degeneration" may be fairly applied without committing ourselves to any statement as to the exact nature of the change, and as to whether it was a primary affection of the vessel wall or followed on the fibrosis above mentioned.* What the chemical nature of this change is seems to be quite uncertain; indeed, the different names applied to it—"hyaline," "colloid," "amyloid," "mucoid"—might lead one to suspect as much. I have tried to colour this substance with the stains for amyloid disease (on hardened material, however), and also with those for mucin, but have never obtained any result. It stains pink with v. Gieson's fluid.

It seems probable then, that more than one type of change may be present in the retinal vessels. We may

* An example of what may be regarded as true hyaline degeneration in the retinal vessel walls will be found described and figured by Mr. Spicer and Mr. Parsons in the Trans. Oph. Soc., 1902, p. 306, Pl. XXII, fig. 1, p. 310.

have the intima taking the chief part as in the arteries in Case I, and in the vein far back in the nerve in the same case. To this the terms "endarteritis" or "endophlebitis" may be fairly applied if we keep clearly in mind that there is no evidence of inflammation in the ordinary sense (round cell infiltrations or cicatrisation), but merely of proliferation. Then again we may have the connective tissue of the wall playing the chief rôle as, for instance, in the vein in Case III, central to the obliterated portion (fig. 10). To this the terms "arteritis," "periarteritis," "phlebitis," and "periphlebitis" may be applied, again keeping in mind that there is seldom much proof of inflammation. We may also of course have combinations of these two conditions as in the retinal veins in Case I. In addition to these forms we may have, whether as a primary disease of the vessel wall or as a consequence of such changes as the above, the condition known as hyaline degeneration. We may also have the appearances produced by the organisation of thrombi within the vessel lumen, but this, of course, is not a primary disease of the vessel wall.

It is likely that such thickenings of the vessel wall do not lead to hæmorrhage at the actual point of thickening. The wall will be rather strengthened at this point, for there is no reason to think that the new-formed substance is any weaker than the original wall. The hæmorrhages are no doubt produced by the damming back of the blood owing to the narrowing of the lumen, and by the giving way either of unthickened veins more peripherally, or of capillaries which are incapable of much thickening.

The question has been more than once raised how much of the condition of the vessels described above was primary, *i.e.*, was present before any hæmorrhages or dimness of vision had occurred, and how much was secondary to impeded venous flow from thrombosis and glaucoma, and to the general prejudicial effects of continued high tension on the intra-ocular structures. Some observations by Hertel* are of

* Hertel, *loc. cit.*

importance in this connection. Struck with the difficulty just mentioned of telling primary from secondary lesions where a hindrance to the ocular circulation has lasted for some time, Hertel examined microscopically seventeen eyes from persons who had general arteriosclerosis, but no ophthalmoscopic evidence of angiosclerosis, and also a number of eyes from persons who had neither general arteriosclerosis nor ophthalmoscopic changes. He describes two kinds of change. Firstly, an increase of the elastic tissue of all the coats of the vessels, with a tendency to splitting of the elastica interna into more than one layer, but without any definite narrowing of the lumen of the vessel. Secondly, localised bulgings into the lumen consisting chiefly of proliferated endothelial cells with new-formed elastic fibres among them, and proliferation of the sub-endothelial tissues. The first of these changes he regards as not truly angiosclerotic, but merely senile, because in the examination of normal eyes of different ages he found a very definite increase in the elastic tissues from childhood to manhood, and, to a less degree, from manhood to old age (a fact which a few observations of my own tend to confirm). The second group of changes Hertel regards, however, as really pathological, and as being the changes which precede and produce the retinal hæmorrhages of old people. An interesting point in his observations is that he found these changes tolerably advanced in eyes which showed no evidence whatever ophthalmoscopically of any vascular disease. Hertel dealt chiefly with the arteries, but there is no doubt that such changes also occur in veins. Figs. 1, 2, and 3 from Case I show very extensive disease in retinal veins, yet hæmorrhages had only been present for 3 weeks, and glaucoma for 1 week. It is probable, therefore, in this case that there had not been time for the development of any very extensive changes in the retinal vessels, and that the condition shown in these figures approximately represents the condition present while the eye was still a normally functioning organ.

In conclusion, I have to thank the following gentlemen

for gifts of material, and for permission to use cases under their care, viz., Mr. Treacher Collins for Cases I and III, Mr. Simeon Snell for Case II, Mr. Percy Flemming for Case IV. I have also to thank Mr. J. Herbert Parsons for the use of the hospital's excellent microphotographic apparatus.

DESCRIPTION OF PLATES.

CASE I.

FIG. 1.—A small artery and vein on the papilla, stained with Weigert's elastic tissue stain $\times 120$. The artery is the vessel to the right. Abundant elastic tissue in its wall, within which proliferated intima is seen, greatly and eccentrically narrowing the lumen. Vein has extremely thick wall and narrow blood-filled lumen, and fails to take on elastic tissue staining.

FIG. 2.—A retinal vein $\times 120$. Wall enormously thick and lumen very small. Inner layer more granular and with more abundant rounded nuclei; outer more homogeneous and with scantier, more elongated nuclei. Dilated circumvascular lymph spaces. Coagulated exudate in retina. Membrana limitans interna unbroken.

FIG. 3.—A portion of the central vein within the nerve, stained with Weigert's elastic stain $\times 200$. Many wavy elastic fibres in the wall, but no true crenated membrane. Within this, thick proliferated intima with scanty pale nuclei. The lumen lined with a fairly even layer of endothelium. A little piece of the arterial wall is also seen.

CASE II.

FIG. 4.—Thrombus in a retinal vein $\times 100$. Large rounded mass with scattered groups of nuclei, separated from surrounding tissues by a cleft for about two-thirds of circumference, connected by nucleated, young connective tissue in the remaining one-third. Limitans interna intact, bulged towards vitreous. Internal nuclear layer bowed outwards. Abundant hemorrhage in retina. Small artery out of focus to right.

FIG. 5.—Central vessels $\times 120$. Artery shows endarteritis—the crenated membrane can be seen outside the eccentric nucleated thickening of the intima. Lumen lined with intact endothelium. Vein of normal size. Lumen divided into loculi containing blood, by thin trabeculae continuous with tissue of wall and lined by endothelium. No cellular infiltration of surrounding tissues.

FIG. 6.—Central vessels a few sections central to last $\times 120$. Artery as before. Little piece of organised tissue in centre of lumen of vein, lined with endothelium externally, and has in its centre a very small lumen also containing blood and lined with endothelium. Main lumen of vein contains blood, and has also a layer of endothelium. A small twig is entering from the surrounding trabeculæ.

CASE III.

FIGS. 7 to 10 show sections in order from before backwards, but all the sections of the series are not reproduced. The central vein on the tissue in its position is in each case at the top of the figure.

FIG. 7.—Central vessels $\times 170$. Artery contains blood, has large lumen, and shows no endarteritis. Vein lumen rather small, but no endothelial proliferation. Contains a homogeneous coagulum, whose edges are infiltrated with leucocytes, while its centre remains free. No blood in rest of lumen. Surrounding tissues condensed.

FIG. 8.—Central vessels $\times 170$. Arterial lumen smaller. Vein represented by a little knot of cellular new-formed connective tissue with, however, a trace of the old lumen left at each end of it. No infiltration of surrounding tissues.

FIG. 9.—Central vessels $\times 170$. Artery shows some endarteritis. Position of vein represented by the somewhat more cellular connective tissue at the top of the figure. Into this tissue a very small vessel is seen entering. On the other side of the artery is a collateral vein, which has come in from the trabeculæ of the nerve, and has turned back to accompany the artery. It will subsequently cross to the other side of the artery and help in the restoration of the lumen of the vein. It contains some coagulum infiltrated with leucocytes and plastered up against one wall.

FIG. 10.—Central vein $\times 170$. A narrow lumen has been restored, and now contains not coagulum, but formed blood corpuscles, showing that an active circulation was going on in it. The wall is extremely thick, has a faint fibrillar structure, and shows scanty nuclei. The vein has separated a little from the artery, only a small portion of which is shown.

FIG. 11.—The central artery stained with Weigert $\times 90$. Very thick crenated membrane. Within this a fine feltwork of new-formed elastic fibres, which at one place is separated from the crenated membrane by a clear area in which blown-out and vacuolated cells are found. The vein is obliterated at this spot; the place where it should be is towards the top of the figure.

CASE IV.

FIG. 12.—Central vessels at level of lamina cribrosa $\times 100$. Artery, somewhat obliquely cut, is filled with coagulum and red blood corpuscles. There is no vein, unless the little slit in the connective tissues to the right represents it.

FIG. 13.—Central vessels a few sections farther back $\times 100$. The coagulum in the artery has shrunk somewhat and pulled away the crenated membrane—a *post-mortem* appearance. Two little venous twigs are joining to re-form the central vein (a little septum will be noticed between them). These twigs are filled with well-formed blood corpuscles.

FIG. 14.—Central vessels far back in the nerve $\times 100$. The artery is small and shows much endarteritis. Within its lumen there is an organised cellular plug, separated from the proliferated intima by a cleft in which there are some red blood corpuscles. The crenated membrane is faintly visible outside the thickened intima. The vein lumen is quite restored by the accession of collaterals.

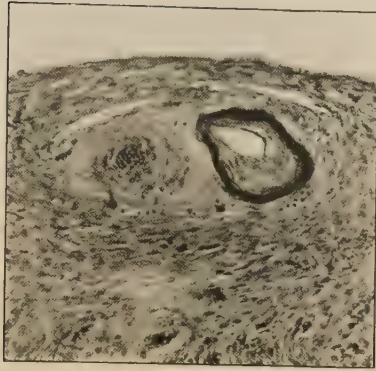


FIG. 1. $\times 120$.

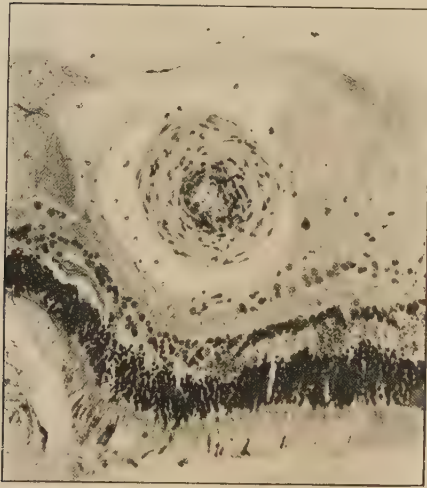


FIG. 2. $\times 120$.

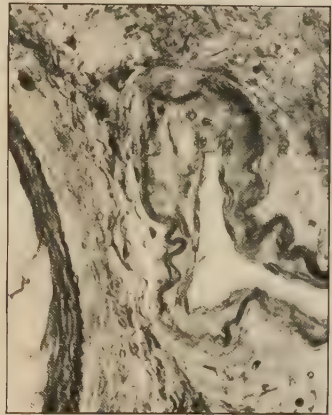


FIG. 3. $\times 200$.

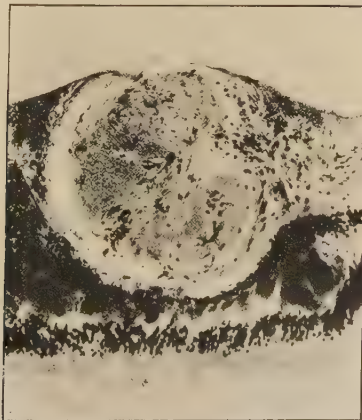


FIG. 4. $\times 100$.

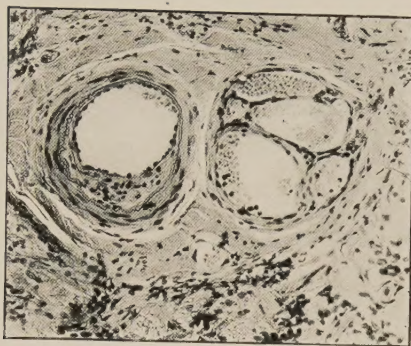


FIG. 5. $\times 120$

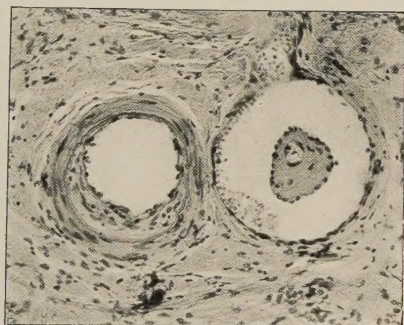


FIG. 6. $\times 120$.

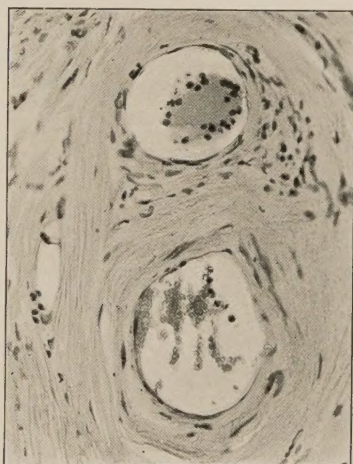


FIG. 7. $\times 170$.

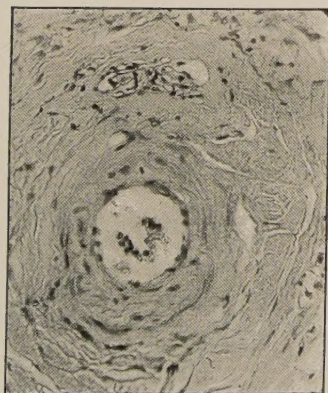


FIG. 8. $\times 170$.

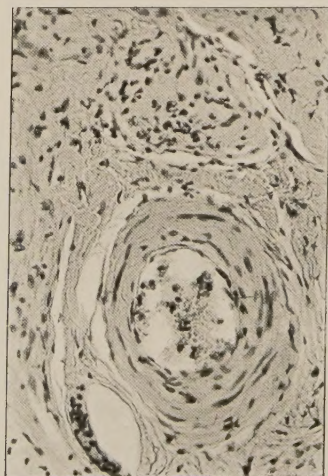


FIG. 9. $\times 170$.

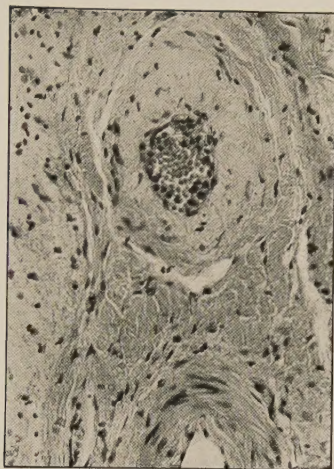


FIG. 10. $\times 170$.

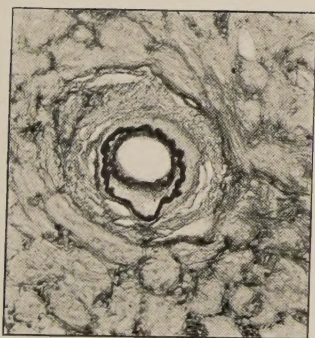


FIG. 11. $\times 90$.

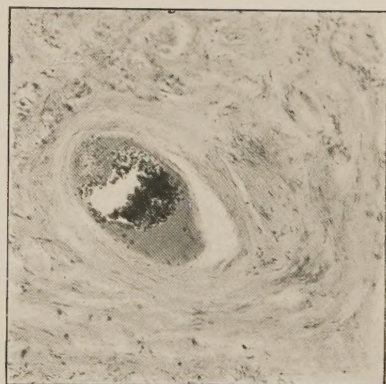


FIG. 12. $\times 100$.

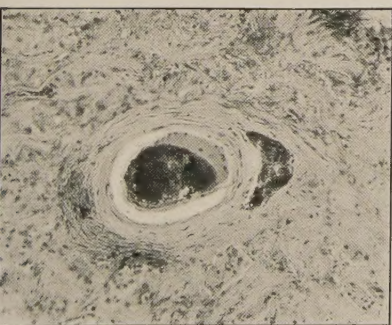


FIG. 13. $\times 100$.



FIG. 14. $\times 100$.

